CHOICE & CHALLENGE

Global Teamwork
In Developing
A Contraceptive Implant

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Global teamwork in developing a contraceptive implant

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By publishing this book, the International Development Research Centre does not intend to promote a particular contraceptive. Mention of a proprietary name does not constitute endorsement of the product and is given only for information.

Abstract — The research, development, and introduction of a new contraceptive, NORPLANT,* was made possible through the skills and commitment of biomedical, public-health, and social scientists in many countries combined with the technical support and funding provided by international nonprofit organizations, donor agencies, pharmaceutical companies, and institutions and organizations in the developing world. NORPLANT is a small device that, when implanted under the skin, provides a woman with protection against conception for 5 years, helping to fill a gap between short-range methods and sterilization. The capsules can be removed at any time, making the method easily and quickly reversible. Recognizing that no one method answers all contraceptive requirements, an international team of researchers successfully increased the contraceptive choices available to women. This technological innovation, NORPLANT, involved a sustained, worldwide research effort, building on existing technologies and past experience to create a new contraceptive and a program for global dissemination. The ultimate success of a health-care innovation, such as NORPLANT, demands careful attention to building national delivery systems capable of managing the distribution and application of the new technology. Any family-planning method demands equal attention to the concerns of the user and the provider. Decision-makers, health-care providers, and scientists should be aware of the challenges that confront this kind of innovative development.

Résumé — La mise au point et l'introduction d'un nouveau contraceptif, NORPLANT,† ont été possibles grâce au savoir et à l'engagement des spécialistes de la biomédecine, de la santé publique et des sciences sociales de nombreux pays en développement et à l'appui technique et au financement d'organisations internationales sans but lucratif, d'organismes d'aide, de compagnies pharmaceutiques et d'établissements et organisations du Tiers-Monde. NORPLANT est une capsule médicamenteuse qui, une fois introduite dans le tissu sous-cutané, protège la femme contre la conception pendant 5 ans. L'implant comble en partie le vide qui existe pour l'instant entre les méthodes de contraception à court terme et la stérilisation. Après enlèvement de la capsule, ce qui peut se faire en tout temps, la femme redevient vite fertile. Le livre décrit comment une équipe internationale de chercheurs, conscients qu'aucune méthode ne répond à tous les besoins de contraception, a réussi à accroître le choix des moyens contraceptifs offerts aux femmes. Il a fallu des recherches mondiales soutenues, inspirées des technologies existantes et de l'expérience, pour créer ce contraceptif nouveau et le programme qui le diffuserait dans le monde entier. Le succès éventuel d'une innovation comme le NORPLANT exige que l'on établisse très soigneusement des systèmes nationaux capables d'en gérer la distribution et l'application. Il faut que toute méthode de planification familiale traduise tant les préoccupations de l'utilisatrice que celles du fournisseur. Les décideurs, les travailleurs de la santé et les scientifiques doivent être conscients des défis qui sont dans le sillage de telles innovations.

Resumen — Gracias a la experiencia y dedicación de científicos de muchos países trabajando en los campos de la biomedicina, salud pública y sociología, fue posible hacer investigaciones y crear e introducir en el mercado un nuevo contraceptivo conocido con el nombre de NORPLANT.‡ Estos científicos han contado con la ayuda técnica y el financiamiento proporcionados por organizaciones internacionales con fines no lucrativos, agencias donantes, compañías farmacéuticas e instituciones y organizaciones del mundo en desarrollo. NORPLANT es un dispositivo pequeño que, cuando se implanta bajo la piel, proporciona a las mujeres protección contra embarazos durante 5 años. Este contraceptivo ayuda a llenar el vacío existente entre los métodos contraceptivos a corto plazo y la esterilización. Las cápsulas se pueden retirar en cualquier momento, lo que permite neutralizar con facilidad y rápidamente los efectos de este método. El libro describe cómo un equipo internacional de científicos, reconociendo que ningún método satisfacía todos los requisitos de la contracepción, amplió la gama de contraceptivos disponibles para mujeres. Esta innovación tecnológica bajo el nombre de NORPLANT requirió un esfuerzo investigativo mundial constante, el cual estuvo basado en tecnologías existentes y experiencias pasadas con el fin de crear un nuevo contraceptivo y el programa para difundirlo mundialmente. Para que tenga éxito una innovación en el campo de la atención médica, como es el caso de NORPLANT, es necesario prestar cuidadosa atención a la creación de sistemas nacionales capaces de administrar la distribución y aplicación de la nueva tecnología. Cualquier método de planificación familiar exige que se preste igual atención a las interrogantes del usuario y a las del que distribuye el producto. Los encargados de tomar decisiones, los que prestan atención médica y los científicos deben estar conscientes de las dificultades que surgen cuando se está en presencia de una innovación de este tipo.

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* NORPLANT is the registered trademark of the Population Council for contraceptive subdermal implants.

† NORPLANT est la marque déposée du Population Council pour les implants contraceptifs sous-cutanés.

‡ NORPLANT es la marca registrada del Consejo de Población para contraceptivos subcutáneos.

Acknowledgments

As with most of the NORPLANT experience, this publication has been a collaborative effort extending over several years. Research, writing, and editorial services were provided by Jane Alexander, a science writer and editor; Sandra Waldman, Manager of Public Information for the Population Council; and science writer Bob Stanley, who revised the work for IDRC. Within IDRC, Terry Smutylo of the Office of Planning and Evaluation was responsible for overall coordination of the project.

The contributions to this publication of the following members of the NORPLANT team are greatly appreciated: Frank Alvarez, Wayne Bardin, George Brown, Judith Bruce, Ethel Churchill, Horacio Croxatto, Juan Diaz, Soledad Diaz, John Gill, Forrest Greenslade, Soili Jarvela, Harold Nash, Dale Robertson, Irving Sivin, Joanne Spicehandler, Rosemarie Thau, Beverly Winikoff, and George Zeidenstein.

Development of NORPLANT would not have been possible without the cooperation of thousands of women who volunteered to use the new contraceptive and reported their experiences to clinic investigators — their contribution is gratefully acknowledged.

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Foreword

This publication documents the research, development, and introduction of a new contraceptive. It is the story of NORPLANT, a small device that, when implanted under the skin, provides a woman with reversible protection against conception for 5 years. The effort to bring NORPLANT implants from the laboratory to the family-planning program spans more than two decades.

It is also the story of an extraordinary, worldwide collaborative effort to make this project happen. The Population Council combined the skills and commitment of biomedical, public-health, and social scientists in many countries with the technical support and funding provided by international nonprofit organizations, donor agencies, pharmaceutical companies, and institutions and organizations in the developing world. All these elements produced a program of great breadth, with strong scientific research elements, and innovative field operations. None of this would have been possible without the cooperation of thousands of women who volunteered to use the new contraceptive and reported their experiences to clinic investigators.

The Population Council is indebted to the International Development Research Centre (IDRC) of Canada, a long-time supporter of the Council's contraceptive research efforts, for encouraging and publishing this history of the NORPLANT program. (NORPLANT® is the registered trademark of the Population Council for contraceptive subdermal implants.) Through this joint project, the Council and IDRC are attempting to inform decision-makers, health-care providers, and scientists of the challenges that confront this kind of innovative contraceptive development. It is our hope that this account of the story of the development and introduction of NORPLANT — the mistakes as well as the achievements — will benefit other organizations working with new technology.

Four overriding themes emerge: that there is a continuing need for new contraceptives; that a sustained,

collaborative effort is required to develop them; that a comprehensive program of introduction is needed to facilitate the widespread use of new contraceptives; and that ultimate acceptance of any family-planning method demands equal attention to the concerns of the user and the provider.

George Zeidenstein
President
The Population Council

Preface

IDRC has supported research by the Population Council since 1973. Through its contribution to date of about 6 million dollars, IDRC has been part of the international effort directed by the Population Council that has produced the innovation in contraceptive technology known as NORPLANT. At this point, NORPLANT is available in close to 50 countries around the world, and approval by the US Government's Food and Drug Administration is expected by mid-1990. This is a good time, therefore, to examine how NORPLANT was created and why it is spreading so rapidly around the world, and to draw lessons useful to others working in this or other fields of technology development. The NORPLANT story illustrates examples to be emulated and pitfalls to be avoided. Overall, we believe it gives a fascinating insight into the development and dissemination of a promising new technology.

Technological innovation is seldom linear. It involves people working on different problems in different places at different times. This makes it a difficult process to understand and even more difficult to influence. By presenting the NORPLANT example, we hope to help those who seek to understand or manage research so that research can be more effective in bettering the lives of its intended beneficiaries.

The story portrayed in this book demonstrates: the importance of a long-term commitment; the fragile chain of choices linking success and failure along the way; and the vulnerability of a new technology to events and pressures in the social and economic context in which it is developed or applied. It also illustrates how careful planning, sustained effort, and fortuitous events interact, to carry a technology forward and overcome problems.

The goal of this book is not to promote a particular contraceptive, but to learn more about how technologies come into being and how one can positively influence that process. We hope this case study will help national decision-makers examine their own expectations for their

national research programs more realistically; and we hope to inspire researchers with the creativity and tenacity demonstrated over the years by those who contributed to the development of NORPLANT. We also feel this story illustrates the value of contact and exchange among scientists and the importance of adapting the delivery of a technology to each environment in which it is expected to function.

Finally, we would like to recognize that the NORPLANT story is far from over. As this particular technology is rapidly being diffused throughout the world, researchers are working to refine and improve it. It is obvious that, in the rapidly changing technological world around us, no technology is ever finished. It keeps evolving and adapting as more is learned about its capabilities and its limitations through actual application. What often determines the ultimate success of a technology is the ability of its users to build on its strengths and reduce its limitations. From its inception, IDRC has recognized the need for indigenous scientific capacity to manage the introduction and adaptation of knowledge and technologies in the development process. The NORPLANT story gives a very clear illustration of how important this is. A cornerstone in the global dissemination of NORPLANT is the careful development of national capacity and self-reliance in promoting and applying this technology. Clearly recognizing this, the Population Council has implemented a plan designed to ensure that the technology is correctly used and understood, and to feed back information on problems that may arise to those who are in a position to improve the technology further.

IDRC is proud of its participation in this international team effort and, by publishing this book, wishes to make the insights and lessons learned available to others in similar fields of technological innovation.

Richard Wilson
Director, Health Sciences Division

W. Doug Daniels
Director, Office of Planning and Evaluation
International Development Research Centre

The need for new contraceptive options

Most nations of the world now have policies that support family planning programs. That could not be said even two decades ago. The shift in attitude and behaviour toward limiting family size has occurred much faster than most other kinds of social change, facilitated in great part by modern developments in contraception. As the desire to space and limit the number of children becomes more prevalent, so too does the need for more acceptable and effective contraceptives for both women and men.

When John D. Rockefeller 3rd founded the Population Council in 1952, none of the modern methods of family planning existed. The very notion of family planning was extremely sensitive: an idea that had little public or political support anywhere in the world, including the USA.

Convinced that too rapid population growth constituted a threat to people and nations, Rockefeller formed an independent, nonprofit organization to study the interconnections between demography, reproductive physiology, and family planning in the developing world. Offering grants to researchers at a time when little money was available from other sources, the Council helped to establish the legitimacy and respectability of family planning and to focus the attention of world leaders on the relationship between fertility and economic and social development.

Initially the Council's Biomedical Division (now the Center for Biomedical Research) had no laboratories, and concentrated on grant and fellowship programs that, by supporting basic and applied research, could accelerate development in contraception. The Council quickly recognized, however, that it could influence the direction of research more effectively if it assembled its own practicing scientific team. The Council established its biomedical research laboratory in 1956 at the Rockefeller Institute for Medical Research (now the Rockefeller University) in New York City.

The era of modern contraception, which began in 1960

The Population Council

The Population Council, an international, nonprofit organization established in 1952, undertakes social and health science programs and research relevant to developing countries and conducts biomedical research to develop and improve contraceptive technology. The Council provides advice and technical assistance to governments, international agencies, and nongovernmental organizations; it disseminates information on population issues through publications, conferences, seminars, and workshops.

Howard Tatum who, while at the Population Council, invented the T-shaped IUD.

with the marketing of oral contraceptives, spawned revolutionary changes in attitude. Women could control more easily and effectively when and whether to have babies. "The Pill" offered a method that was comparatively easy and convenient, relatively safe, reversible, and highly effective when properly used. Today, it is the most widely used form of reversible contraceptive. However, oral contraceptives are not appropriate for every woman, so continued research was, and still is, needed into other promising contraceptives.

The Council's work focused on the development and testing of contraceptives that were seen to be particularly suitable for use in developing countries. The criteria for such contraceptives were that they should be safe, long acting, inexpensive, easy to use, reversible, convenient, and appropriate for large-scale family-planning programs.

During the 1960s, the Council demonstrated the safety and effectiveness of plastic intrauterine devices (IUDs), notably the Lippes Loop. The Council's first substantive contribution to new contraceptive technology was the successful development of a more effective IUD, a small T-shaped plastic device wound with copper wire. The introduction of the Copper-T 200 in 1973 gave the Council staff first-hand experience in the provision of a new, low-cost contraceptive in developing countries. Since then, there have been two more advanced versions of this IUD: the Copper-T 220 and the Copper-T 380. More than 30 million Copper-T 200 IUDs have been distributed by Council licensees in developing countries since their introduction. About eight million Copper-T 380As have been distributed in more than 70 countries since 1982, and this model has been marketed in the USA since May 1988.

The need for a range of options

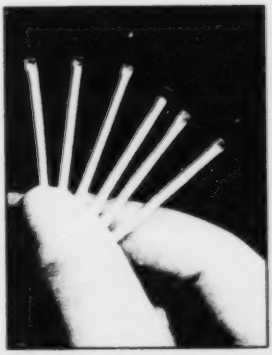
In choosing a contraceptive, a woman weighs the perceived drawbacks and benefits of the method in the scale with the consequences of an unwanted pregnancy. Those perceptions vary from woman to woman. All contraceptive methods have drawbacks or side effects that make them less attractive to some women, and it is likely that they always will. In addition, women may switch from one method to another during their reproductive lives as they grow older and their lifestyles and goals changes. Women also run the risk of unwanted pregnancy even when they use reliable methods, because no method is totally effective.

In short, no contraceptive will to have all the ideal characteristics: a method acceptable to all cultures, that never fails, is reliable and reversible, has no side effects, is easy to use, convenient, cheap, and long lasting. Every woman needs the widest possible selection of methods to improve the prospect that she will find one that suits her current needs. Also, by expanding the array of methods available, family-planning programs improve the chances of reaching the millions of women who are not yet using contraceptives at all.

A promising new entry to the list of available contraceptives is the Population Council's NORPLANT,[1] a convenient, effective, reversible, long-term approach to family planning that helps to fill a gap between short-range methods and sterilization. The method consists of matchstick-sized flexible silicone rubber capsules that are inserted under the skin of a woman's arm. A single six-capsule set of NORPLANT is designed to be effective for 5 years; and it may be removed at any time to permit prompt return to fertility. By releasing continuous, very low doses of a synthetic progestin, NORPLANT does not produce the steroid peaks that follow once-a-day doses of oral contraceptives.

NORPLANT is especially attractive to women who are not absolutely certain that they have finished childbearing, to those who want to space their families, to those who should not use estrogen (a hormone contained in most oral contraceptives, which causes side effects in some women), and to those who have reservations about the irreversibility of sterilization. Like all contraceptives, NORPLANT has side effects, the most troublesome to the user being irregular menstrual bleeding patterns. Because NORPLANT is not going to be accepted by all women — for example, by those who dislike hormonal methods — the need still exists for continued research into other contraceptive methods, for both women and men.

However, the Council's aim of providing a wider range of contraceptive choices to people in developing countries was made even more difficult by events affecting the private sector: increasing costs and fear of litigation have driven most of the major pharmaceutical companies out of contraceptive research. By 1970, it was apparent that most large pharmaceutical companies, which previously had pursued the development of new contraceptives, now found it more profitable to invest their resources in other health-care areas.



A set of NORPLANT *capsules.*

[1] NORPLANT® is the registered trademark of the Population Council for contraceptive subdermal implants.

The gap left by their departure from the field is being filled to some extent by research organizations such as the Population Council, which are funded by international donor organizations. The costs involved in bringing a new contraceptive to market are extremely high. By 1988, the Population Council and its International Committee for Contraception Research (ICCR) had invested about 8.6 million US dollars (USD) on the research, development, and introduction of NORPLANT. They expect to spend another 10 million USD over the next decade to encourage proper use of the method. These figures do not include the costs incurred by the manufacturer or by local institutions collaborating in the program.

The Council's role in taking a product from research through to introduction is unique among nonprofit organizations in the field. Also, the Council has had to raise separate funds for each stage of the project. The major donors to NORPLANT research and development included the Ford, Mellon, and Rockefeller Foundations, members of the Rockefeller family, the George J. Hecht Fund, the US Agency for International Development (USAID), and IDRC in Canada. Major funding for the introduction program came from the Hewlett and General Service foundations, the Finnish International Development Agency, the Population Crisis Committee, USAID, IDRC, and the United Nations Fund for Population Activities (UNFPA).

The mechanism that the Council uses to expand its capability for contraceptive development involves collaboration — first, in forming the ICCR, through which scientists tested efficacy and toxicology in their own clinics and laboratories; second, in forging working relationships with other major agencies in the field; and, third, in enlisting the cooperation of dozens of scientists and institutions in developing countries.

The research, development, and introduction effort by the Population Council for the NORPLANT method, which is documented here, is offered as a reference for future efforts by other nonprofit agencies as well as by the Council. It should not, however, be seen as a blueprint to be followed blindly, because each project will have its own unique requirements. It should serve as an example of good decisions and bad, and — perhaps more important — of the principles that guided the Council's efforts from the beginning of the program.

The role of IDRC

Since 1971, IDRC has been a consistent supporter of both contraceptive research and introduction efforts through contributions to the ICCR and other Population Council activities. In addition to support for basic research on the contraceptive vaccine and implant programs, IDRC has funded significant studies throughout the introduction of NORPLANT, including an evaluation of the method in Indonesia in 1981 and a major 3-year study of the determinants of user satisfaction that started in 1987. IDRC's production of this publication is a logical extension of the organization's interest in communicating the results of research.

Part I
The NORPLANT project

Exploring the concept

The key to the contraceptive implant concept is a polymerized silicone rubber material called Silastic,[2] which was developed by the Dow Corning Corporation for use in artificial heart valves and other medical devices implanted in the body. In 1965, Dr Sheldon Segal, then director of what is today the Council's Center for Biomedical Research, was interested in the material for a contraceptive experiment that involved blocking the oviducts of rabbits. A chance conversation with a Dow Corning representative changed his perspective and began the research that led to the introduction more than 20 years later of NORPLANT.

The man from Dow Corning mentioned in passing that two surgeons had discovered a new property of Silastic while experimenting with heart pacemakers in dogs. Before implanting them into dogs' heart muscles, the surgeons had injected a blue dye into the pacemakers to make them easier to find when removal became necessary. However, when they removed the pacemakers later, no trace of the dye remained — it had dissolved and diffused through the polymer walls. This suggested that Silastic might serve as a reservoir for the long-term delivery of cardiac drugs, an idea that they had tested with encouraging results.

Segal realized at once that, if the product worked for heart drugs, it might also form part of a delivery system for contraceptive hormones. He envisioned a new contraceptive method using silicone rubber implants under the skin, and set out to test his theory the same day. This is how he describes that first experiment on returning to his laboratory.

"I got down some estradiol and mixed it up with liquid Silastic. I injected the material into some castrated female rats and watched them over the next few weeks. Lo and behold, those castrated rats maintained a constant state of estrus." The Silastic was allowing the estradiol to diffuse slowly over a period of weeks, thus extending its expected biological effect.

Silastic is a proven material that has been in use since the early 1950s. The key to making the implant idea

[2] Silastic® is a registered trademark of the Dow Corning Corporation.

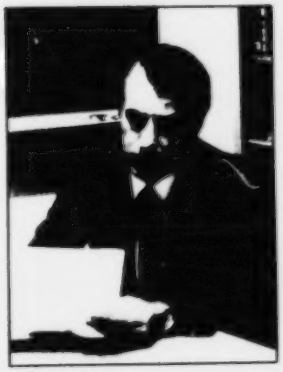
possible, then, lay in finding a steroid that was safe, potent enough so that a small reservoir could supply several years of contraception, and sufficiently soluble in Silastic that it could be contained in implants of practical dimensions.

Steroids — fat soluble molecules that act as messengers in the control of many body processes — include the female sex hormones estradiol and progesterone that, among other things, regulate women's fertility. Synthetic versions, which can be absorbed from oral use, have formed the active ingredients in oral contraceptives since the first version of The Pill was introduced in 1960. Synthetic progesterone-like substances called progestins mimic the action of naturally produced progesterone, which normally appears in the bloodstream after the ovary has released its monthly egg and signals the ovary not to release any more eggs.

In the case of The Pill, researchers began with only a progestin, but later added a synthetic estrogen to suppress troublesome between-period bleeding that progestin alone tends to cause. Scientists at the Council's Biomedical Division ruled out incorporating estrogens into Silastic implants, however, because of reports implicating that hormone in cardiovascular problems such as heart attacks and strokes. In addition, incessant estrogen dosing prevents the uterine lining from sloughing off as it does every month in a normal menstrual period. Women taking combined oral contraceptives get around that problem by interrupting pill-taking for a few days each month. This option was obviously not available in a continuous delivery system such as a subdermal implant.

Other researchers were testing the properties of progestins. One type, chlormadinone acetate, was found to provide a high level of contraception without too much bleeding, reducing the need for estrogen. Progestin-releasing Silastic implants in ewes shortened the sheeps' estrus. In this experiment, the researchers found the steroid's release rate to be constant and dependent on the surface area of the implant and the wall thickness of the capsule, rather than on the concentration of the drug itself.

Segal enlisted the help of Horacio Croxatto, a Chilean scientist who had joined the Council as a Fellow in 1965. Croxatto mixed estrogen crystals and a liquid silicone, added a catalyst to induce polymerization, and injected the mixture into castrated female rats. The results mimicked Segal's original tests, and the rats maintained their weight, while a control group got heavier, as castrated rats typically do.



Horacio Croxatto, Population Council Fellow in 1965–1967 and an early member of the NORPLANT *team.*

Laboratory studies showed that the silicone rubber acted like a solvent even for the dry crystals, allowing continuous release of the steroid.

The capsule concept

However, the release rate of Croxatto's implants varied enormously. The reason became apparent when he examined the animals: the Silastic injections had taken on a variety of shapes as they hardened under the skin. Correctly surmising that the surface area and thickness of the rubber determined release rates of the steroid, Croxatto revised Segal's original implant concept. He recalls: "I got silicone rubber tubing from Dow Corning, cut it into uniform pieces, filled them with steroid crystal, and sealed the ends with Silastic adhesive. That was the origin of the capsule concept."

Silastic's properties exceeded the expectations of both researchers. Not only did the hormones continue diffusing for more than 1 year, but the daily release rate of the steroid was not significantly lower even when the capsule's contents were greatly reduced. This eliminated the concern that the user would receive too much hormone at the beginning and too little at the end of the capsule's life span. They also learned that different steroids are released at different rates.

Determining dosage, thickness, and effectiveness

To determine the rate at which a given progestin diffuses through Silastic, researchers placed steroid-filled capsules in solution, maintained them at a constant temperature, with constant shaking, and finally measured how much steroid had been released from the capsule into the solution over a given period of time. This in vitro work helped establish the surface area and wall thickness needed to release the amount of a particular steroid estimated to produce an antifertility effect in women. To estimate the needed dose, researchers drew upon experience with steroids in combination contraceptives.

Having established the capsule dimensions for a particular steroid, researchers tested various doses, both orally and through implants, first in animals for evidence that the estrus cycle was being inhibited, then with women to gauge the effect on their menstrual cycles. If a woman taking a progestin had low progesterone levels during the second phase of her menstrual cycle, chances were that the progestin had a contraceptive effect. Researchers can measure progesterone levels with the radioimmunoassay, or RIA, an exquisitely sensitive test that measures tiny amounts of biological substances.

Once they had established a dosage that consistently altered the menstrual cycle, the researchers knew they were on the track of a good contraceptive. By correlating release rates with progestin blood levels, they could calculate the number and size of implants needed. For practical contraception in real-world situations, however, drug researchers and clinicians must make allowance for a considerable range of response, since the rate at which different women metabolize steroid hormones varies quite widely.

There was a very real prospect for a new contraceptive technique that would enable a woman to substitute a single visit to a clinic for thousands of days of pill-taking.

In addition, the capsules could be removed at any time, making the method easily and quickly reversible. Council scientists had early decided that, because the implant method would be long lasting as well as provider-dependent, reversibility was important — no matter what the user's reasons. That decision turned out to be fortunate, for later research with NORPLANT revealed that, next to effectiveness, women value the method's reversibility as its greatest asset.

In the first phases of the research, three decisions were made that helped to define the program. The first was to use Silastic for the implant because it was biocompatible (the body would not reject it) and nonbiodegradable (it would not break down in the body). Second was to search for an effective progestin and not to use estrogen. Third was to study the properties of only those progestins that had already been tested extensively by drug companies — thus saving the time and money needed to prove that a new material was safe.

The search for the right progestin

Convinced that their approach was sound, Segal and Croxatto began testing various progestins used in oral contraceptives, seeking substances, daily release rates, and blood levels that were not only safe and effective, but also produced acceptable patterns of menstrual bleeding. They also had to establish diffusion rates that were fast enough to be effective, but not so fast as to exhaust the capsule's supply of progestin too quickly.

In 1967, megestrol acetate, a progestin widely used in combined oral contraceptives, became a leading candidate for the implant, and researchers began focusing on the long-term safety and side effects of implants delivering low doses of this hormone. The Council acquired a licence from the progestin's manufacturer, British Drug Houses Ltd, allowing the Council to use the compound for research purposes and granting it the right to distribute any contraceptive implant it might develop to governments and nonprofit family-planning programs in the developing world.

That year, the Council spent about 0.5 million USD on the implant project. To aid the Council's contraceptive development efforts, the Ford Foundation donated

6 million USD in 1966 to cover work for 5 years, and 1 year later another 1.6 million USD for a primate research colony in the Rockefeller University laboratories to test the long-term safety of implants. With matching grants from members of the Rockefeller family and the Rockefeller Foundation, the funds also enabled the Council's Biomedical Division to arrange for greatly enlarged facilities at the University.

Not everyone working in contraceptive development was supportive, however. There was a good deal of skepticism from some pharmaceutical executives who contended that delivering drugs through implants was an unworkable idea. Others believed that the concept of surgically inserted implants would never be acceptable to women, and had even convinced some funding agencies of that view.

Segal and his colleagues were undeterred. By 1967, they had enough assurance of safety and efficacy from animal studies to organize pilot studies with women volunteers. Croxatto, back in Chile after 2 years as a Council Fellow, continued his work with implants. He reported the first clinical experience with a progestin released from silicone rubber capsules in 1968, using Silastic tubing and the progestin chlormadinone acetate. The capsules were implanted using large, hollow needles intended for blood transfusions, modified in the clinic's machine shop to serve as trocars to insert the capsules under the skin.

Croxatto began a Phase I or tolerance study with a group of 25 women volunteers, inserting single-capsule implants that delivered very low doses of the progestin. He was pleased to find not only that the women readily accepted the capsules, but also that they had no infections from the implantation and, as time went on, experienced normal menstrual periods and no side effects.

At about that time, however, the US Food and Drug Administration (FDA) began preparing to remove chlormadinone acetate from the market because of adverse toxic findings in tests with dogs. So the implants had to be removed, and Croxatto and his volunteers had to begin again, using capsules containing megestrol acetate. This time, three other former Council Fellows — in Brazil, India, and Italy — also started trials, each involving 25 women. All four trials showed the same results: the doses of progestin were too low to provide acceptable levels of protection.

They would have to use higher doses or more potent progestins to make the method more effective. However, all believed that implanting more than four capsules would not be acceptable. They were surprised to discover that they were wrong: women generally did not balk at receiving more than four capsules when the trade-off was an effective, long-term protection from pregnancy.

Recalling those early studies, when the research proceeded on a basis of trial and error, Croxatto pays tribute to the perseverance of those first women volunteers: "How we suffered when the method failed and volunteers got pregnant. Our gratitude goes out to all the women who participated in the various phases of the studies. With great enthusiasm, they cooperated in an incredible way — keeping records of their bleeding for months and months, giving many blood samples, and allowing us to take biopsies."

Developing the implant

The early research results were so encouraging that Segal decided they were ready to begin the product-development phase. With this in mind, the Council sponsored the first International Workshop on Implant Contraception in New York in December 1968 — only 3 years after Segal's first experiment.

One outcome of that meeting was that the Council granted a total of 0.3 million USD for implant-related research — considered a large sum at the time — to investigators in Austria, Brazil, Chile, Finland, Guatemala, Italy, Nigeria, the Philippines, Taiwan (China), and the USA. The researchers were to study such issues as required dosages; effects on carbohydrate metabolism and liver function; hormone diffusion rates; long-term safety in dogs, sheep, and monkeys; and acceptability to women and men. (At that time, the Council was also conducting research on the utility of implants for male contraception.) The Council also supported training for researchers from several countries in laboratory techniques involved in developing implants. In 1969, about 0.5 million USD was again devoted to the development of NORPLANT.

Sheldon Segal in the laboratory (early 1970s).

By mid-1969, results of the small clinical trials showed that a daily release rate of 100 µg from four implants containing megestrol acetate provided effective contraception without interfering significantly with the menstrual cycle. The scientists still hoped for a lower dosage of hormone, however. While continuing its studies on megestrol acetate, the Council also arranged with Wyeth International (a division of American Home Products Corporation) to gain access to the highly potent progestin, norgestrel, in the hope that it would diffuse satisfactorily through the walls of Silastic capsules. This was to prove to be a decision of immense importance.

Norgestrel, which is many times more potent than natural progesterone, is one of the most widely used oral-contraceptive hormones. The Population Council's licence arrangement with Wyeth was similar to the one

drawn up with British Drug Houses for megestrol acetate. Like many compounds, norgestrel comes in two forms, each a mirror image of the other in shape. Only one form, the levorotatory (or left-handed) form is biologically active. Because levonorgestrel makes up 50% of ordinary norgestrel, it appeared that using it alone would enable the scientists to load more active material for a longer lifetime into fewer capsules.

Expanding the team

By 1970, the Biomedical Division had developed into one of the major research facilities in the world concentrating on problems of reproductive physiology. Segal's reputation and personality were such that, as director of the Division, he was able to assemble a strong and enthusiastic team to press ahead toward the goal of a marketable product.

At the same time, it became apparent to Segal that completion of the implant project needed a major effort and that leads on other possible contraceptives were not being pursued. He sought the views of colleagues in many countries on the best approach to developing new contraceptives, such as implants. In response to their suggestions, he assembled an international group of scientists who would work as Council consultants in their own laboratories in a collaborative effort to pursue promising leads. The members of the group were carefully chosen: each was a physician who had worked with Segal

Devising the technology

To prepare capsules for the initial trials, Council biochemist Dale Robertson had to devise a way to get the dry crystals into the tiny opening of the relatively long and flexible capsules. After trying various methods, including mixing the crystals into slurries, he and his technician hit on a system that worked.

The crystals had to be the right size — too coarse and they would not pack into the capsule properly, too fine and they would not pour at all. Robertson inserted the tip of a tiny funnel into one end of a capsule, weighed out the right amount of the steroid, poured it in, and then vibrated the crystals into the capsule by rubbing a pocket comb across the rim of the funnel. A more rapid way to fill the capsules was developed in the early trials, and the comb-vibrator was replaced by metal-engraving tools specially modified by an instrument maker at the Rockefeller University. Capsules for the early trials were made by hand by a pharmaceutical company in Mexico. Later still, a small-scale manufacturing apparatus was developed and set up at the plant of the Finnish pharmaceutical company selected to produce sufficient quantities of the capsules for the multinational clinical trials scheduled to begin in 1975.

before, was located at a research clinic, and had a strong interest in endocrinology and human reproduction.

These were the first members of the Council's International Committee for Contraceptive Research (ICCR).[3] One reason for the international approach was to gain experience in a variety of cultures with methods that were expected to serve contraceptive needs worldwide. By organizing the ICCR, the Population Council had created, in effect, an international network of clinics and laboratories.

ICCR members agree to devote a substantial portion of their time to initiating and investigating each promising contraceptive lead with administration provided by Council staff. The concept is simple: each member assumes primary responsibility for one method, initiating studies of effectiveness, safety, and mechanism of action, and collaborating with other members on research that might benefit from a combined effort. Thus, while remaining at their home institutions, some of the world's most talented investigators in the contraceptive field could cooperate effectively on new enterprises. These activities are supplemented by investigations conducted in the Council's own laboratories, and through contracts with other clinics and laboratories.

Assured of 5 million USD in grants over 3 years from the Ford and Rockefeller foundations, the ICCR, at its first meeting, in December 1970, selected eight potential new contraceptive methods for more intensive study. High on the list was a long-lasting, reversible contraceptive implant for women.

Because the program had to involve extensive clinical testing, rules were established to assure the rights and welfare of the women who participated in those trials. These rules, set forth in 1971, have been upgraded since as researchers throughout the world have become increasingly aware of the need for rigorous procedures to assure the welfare of those who participate in clinical trials. At the heart of those rules is the need for informed consent from the patient after the risks and benefits of the research have been outlined, as well as continuing review of the propriety of the protocols and the methods used to obtain informed consent.

One of the ICCR's first undertakings was an extensive program of Phase II, or effectiveness, studies of various progestins in different doses. By 1974, the ICCR was testing

[3] Current members of the ICCR — Philippe Bouchard, Horacio Croxatto, Tapani Luukkainen, Daniel Mishell, and Pran Talwar. Former members of the ICCR — Elsimar Coutinho, Aníbal Faundes, Julian Frick, Elof Johansson, Earl Plunkett, and Regine Sitruk-Ware.

At an ICCR meeting, some members with Council staff (left to right, Horacio Croxatto, Alfred Moo-Young, and Rosemarie Thau).

eight different progestins in 36 dosages on 1 100 women. The goal was to identify which progestin best combined high effectiveness at the low dose with minimum undesirable side effects. In October 1974, Croxatto and his colleague Soledad Diaz initiated the first trial of levonorgestrel using six capsules, each containing 36 mg. The low release rate of levonorgestrel made the use of six capsules necessary but, in turn, offered the promise of a long period of effectiveness. This was the pilot study for NORPLANT.

The randomized, double-blind study

At the end of 1974, the ICCR reviewed results of all pilot tests; three strong candidates emerged for subdermal implants — megestrol acetate, levonorgestrel, and norgestrienone, another potent progestin. Several others were eliminated either because pregnancies occurred or because they were reported to cause breast nodules in dogs. The Committee agreed to begin a large, randomized, double-blind clinical trial, one of the milestones in the development of NORPLANT — the decision on whether to introduce a new contraceptive method to the general public ultimately rests on the method's performance in clinical trials. Such trials must be carefully planned, and the outcomes accurately recorded and meaningfully analyzed.

As chief investigators for the studies, the committee chose the heads of five family-planning clinics — in Brazil, Chile, Denmark and Finland combined, the Dominican Republic, and Jamaica. Each would recruit 300 women, for a total of 1 500. One-third of each group, selected at

random, would use one of the three progestin implants — in looking for small differences in effectiveness among highly effective methods, studies of at least this size are needed. To ensure that there was no bias on the part of doctors, scientists, or recipients, none knew which type of implant each woman received. The study was designed to last 1 year, because the investigators did not know how much longer than 1 year the implants would remain effective.

Beginning in July 1975, volunteers were sought among women coming to the five clinics for contraception. They were told, in general terms, about the implants and asked if they would be interested in taking part in the trial. As in most such clinical trials, participants were motivated not by monetary or other material rewards, but by the prospect of helping in the development of a new contraceptive, and by the extra personal care they would receive during the trial.

Women who expressed interest were told that the purpose of the trial was to learn more about an experimental method whose effectiveness and side effects were still not clearly known: that some women might get pregnant; that some might experience irregular bleeding or spotting, or long periods without bleeding; and that others might experience side effects similar to those associated with oral contraceptives. Candidates had to agree to physical and gynecological examinations, and be willing to return to the clinic at regular intervals to discuss their experiences, any problems they might have, and to undergo physical examination. Participants must keep daily records of menstrual bleeding on specially prepared calendars; and they must agree not to use any other method of contraception during the trial. They could, however, request removal of the implants at any time.

To ensure that they would get meaningful information on effectiveness and side effects, the investigators applied strict criteria in choosing participants. Women had to be between the ages of 18 and 35, of proven fertility, not pregnant or breastfeeding, and sexually active. If a woman agreed to participate, met all the criteria, and examinations were satisfactory, she was enrolled. Within 1 week of the beginning of menstruation (to ensure that she was not pregnant), a doctor or clinician would insert six implants in a fan-shaped pattern on the inside of her forearm. Later, the inside of the upper arm was judged the best location, particularly for thin women, although in some countries the lower arm is used instead.

"Our approach is to counsel health workers, who counsel women, not to be overly promotional with NORPLANT. The method is not suitable for every woman." *Joanne Spicehandler.*

Megestrol acetate withdrawn

Shortly after the study began, megestrol acetate was withdrawn from the market by its British manufacturer because, like chlormadinone acetate, it had an adverse effect in studies of toxicity in beagles. Although the ICCR was not convinced that enough data existed to warrant eliminating megestrol acetate, the scientists had no choice but to recommend removal of the implants in January 1976. Because the Council had been studying other promising progestins as well, the removal of megestrol acetate was not as harmful to the program as it might have been had the steroids been tested one at a time.

By October 1976, it was clear that the lifespan of levonorgestrel implants might be several years, while the norgestrienone implants would last less than 2 years. The investigators were tempted to change the rules to allow the women with levonorgestrel implants to keep them longer than originally planned. Extending the study for one of the progestins, however, would mean compromising the study's double-blind aspect for both implant methods. So they lengthened the trial to 15 months for both methods. In February 1977, implant trials in Scandinavia were halted when the pregnancy rate for women using the norgestrienone capsules soared.

By May, 18 months into the trials, it was clear from measuring the amount of steroid remaining in the capsules after removal, that levonorgestrel promised an implant lifetime of several years. Moreover, in implant form it appeared to rank among the world's most effective contraceptives, second only to surgical sterilization. Pregnancy rates associated with its use were less than 1/100 women per year. Norgestrienone, by contrast, had a shorter lifetime and a pregnancy rate of 3.5/100 women.

Believing levonorgestrel to be the best candidate for further study, the researchers broke the blind codes. Those women still using levonorgestrel implants — about one-third of the original group — were permitted to continue using the method if they wished.

Levonorgestrel selected

Twelve years had passed since Sheldon Segal first envisioned a new contraceptive delivery method based on silicone rubber implants. He recalls the moment of decision: "By 1977, we had to make a choice between two excellent

contraceptives: one, norgestrienone, offered better bleeding control, but the other, levonorgestrel, provided a longer lifetime and greater effectiveness. In addition, by that time, there were extensive animal and clinical toxicity data on the use of levonorgestrel taken orally because it had become the world's most widely used progestin in oral contraceptives. We made a decision to go with levonorgestrel."

Up to this point, the capsules had been known simply as levonorgestrel implants. It was Harold Nash — recruited by Segal in 1970 to coordinate the Council's contraceptive development effort after a 16-year career in the pharmaceutical industry — who borrowed one syllable from each word and dubbed the new contraceptive method NORPLANT. The name stuck, and in 1979 the Council registered NORPLANT as its trademark for contraceptive subdermal implants.

Moving ahead

The Population Council's decision to use levonorgestrel capsules did not mean that it would stop trying to develop better implants. Even before the first clinical studies showed the efficacy of six capsules containing levonorgestrel, work had begun on a second generation implant — a two-rod version known as NORPLANT-2 — that would be just as effective.

In the original NORPLANT, the steroid is contained in a Silastic tube; the idea behind NORPLANT-2 was to disperse levonorgestrel evenly within a solid rod of Silastic. In principle, the rods are a superior system because they contain a larger amount of steroid per unit length of implant, so that only two implants are required instead of six. This makes for easier insertion and removal, and greater comfort for the user. In addition, the manufacturing process should be less labour intensive and therefore cheaper.

While various sizes and formulations of rods and steroids were being tested, the problem of designing a practical method of manufacturing them fell to the Council's Dale Robertson, the biochemist who had earlier devised a technique for getting dry levonorgestrel crystals into lengths of Silastic tubing to create the original NORPLANT capsules. It proved to be a much tougher assignment.

Robertson first made homogeneous rods by mixing the steroid with Elastomer 382, which contains finely divided silica for strength — the rods had to be tough enough to be removed without breaking. The mixture was pressed into a specially designed mould enabling them to make 100 rods at a time. Although silica made the rods stronger, it also increased its viscosity and the method was not a success.

The silica filler occupied so much of the rod that there was room for only about 25% steroid limiting the effective life of the implants. Moreover, when tested in women, the rods were found to release a hefty dose at the outset that quickly dropped off and continued to decrease with time. Including enough steroid to last several years meant that women would receive higher dose-rates at the outset than

Dale Robertson making NORPLANT-2 rods by injecting a mixture of levonorgestrel and Silastic into a mould.

the researchers thought wise. To make matters worse, the rods tended to break on removal.

Robertson credits a conversation with Howard Tatum, inventor of the Copper-T IUD, for the idea that solved these problems. They would make rods with no filler, thus creating more room for steroid, and enclose them instead in a very thin sheath of pure Silastic. It worked. The sheath, which Dow Corning makes to specifications for the Council, not only allowed the rods to be removed, but also served to meter the steroid — which now made up about 50% of the rod's weight — so that it was delivered at a more constant rate. Because the rods contained greater concentrations of steroid than the capsules, providing higher release rates and hormone levels in the blood per centimetre of length, the ICCR hoped that fewer rods would be needed to remain effective for several years.

By this time, the researchers suspected that the dose rate delivered by the six-capsule system was close to optimum. Following Robertson's presentation on the rod trials at an ICCR meeting, it was suggested that, considering the much larger dosage in the rod experiments, a total of 8 cm in rod form should be regarded as equivalent to the current standard of 18 cm in capsule form. If accepted, this meant that two 4-cm rods could replace six 3-cm capsules. The ICCR decided to test the hypothesis.

Comparative trials

In 1982, a comparative trial of the six-capsule NORPLANT and the two-rod NORPLANT-2 began in Chile, the Dominican Republic, Finland, Sweden, and the USA. If the trials went as expected, and NORPLANT-2 was shown to be as effective as NORPLANT, Council scientists assumed that the rods — because of their greater convenience and lower cost — would become the more widely used and accepted method. By 1986, the data from the clinical studies indicated that the NORPLANT-2 rods were highly effective. Because the dose being delivered was the same as with NORPLANT, the side effects should be the same. Therefore, the Council decided to apply to the FDA for approval of NORPLANT-2.

By the 4th year of the comparative trials, it was apparent that both versions of NORPLANT were not equally effective. Through the 3rd year of use, the pregnancy rate for both methods was the same — less than 1/100 women. In the 4th year, however, there was a disturbing and

unacceptably high incidence of pregnancies in rod users, greater than 6/100 women. In 1986, the Council instructed investigators in countries holding the comparative trials to remove all NORPLANT-2 rods from users at the end of the 3rd year.

The comparative trials presented the Council, the manufacturer, the investigators, and the collaborating organizations with a new set of circumstances: there were now two NORPLANT methods, one lasting 5 years, the other 3. The Council continued compiling data for its application to the FDA on NORPLANT-2, convinced that there would be a market for both versions. Then, in July 1987, the NORPLANT development timetable was dealt another blow — Dow Corning announced that it would cease manufacture of Medical Grade Elastomer 382, the material used to manufacture the rods.

The need to modify NORPLANT-2

The reason for Dow Corning's decision was a requirement by the US Environmental Protection Agency for additional tests in animals. Laboratory studies had shown that 2-ethylhexanoic acid, a component of the catalyst used in vulcanizing the elastomer, caused liver tumors in rats and mice when given in extremely high doses. The rodents developed tumors when exposed to doses nine million times greater than those a woman using NORPLANT-2 could be exposed to based on body weight.

Dow Corning believed that there was no significant risk to human health in the continued use of this ingredient. However, it informed the Council that it had determined "that the projected time and expense of additional testing could not be justified on the basis of current and anticipated sales volume."

The Council immediately conducted a review of the safety for users of NORPLANT-2 rods. Independent experts in medicine, biochemistry, and toxicology reviewed the data on the elastomer. Both they and the Council agreed that the minute amount of this ingredient that could be contained in the NORPLANT-2 rods presented no risk to women using the method. By late 1987, a toxicological group consultation of the World Health Organization (WHO) also concluded that "exposure of women to the maximal amount [of the compound in NORPLANT-2] presents no human toxicological risk." The FDA also released a statement that it had no

objection to the continuation of studies then underway with NORPLANT-2.

The Council decided to continue with ongoing clinical and preintroduction trials where sufficient supplies of NORPLANT-2 existed, but not to start new trials. There was no need to remove rods from any women. Meanwhile, they would attempt to modify the rods using a different elastomer and, at the same time, move ahead as quickly as possible to file for approval of the six-capsule NORPLANT in the USA. In late 1989, the rods were reformulated using another elastomer and comparative clinical trials for efficacy were scheduled for the first half of 1990.

Seeking approval

The Council's application for FDA approval of NORPLANT was delivered in August 1988. At a public hearing in April 1989, the FDA's Advisory Committee on Fertility and Maternal Health Drugs unanimously recommended approval of NORPLANT for distribution.

Preparing that application proved to be a Herculean task, in part because of the huge amounts of data that the program had accumulated from around the world, but also because the FDA had greatly increased its requirements for data and data analysis during the two decades of implant development. The most sweeping changes came in 1979 with the Good Clinical Practices Act, which required a greater degree of documentation than before. Because the Council underestimated the time it would take to provide this additional paperwork, the organization's application to the FDA took longer to prepare than originally estimated. A large pharmaceutical company might employ up to 100 people to gather and process all the information for a New Drug Application. The bulk of the work for the NORPLANT application, by contrast, was prepared by a small group of Council staff, with some assistance from Wyeth International.

Harold Nash (left) and Irving Sivin with the submission to the FDA for NORPLANT.

The FDA requires the inclusion of all data that may bear on the safety and effectiveness of the drug. The submission for NORPLANT included data from preintroduction evaluations or clinical trials in 44 countries. Studies reported on in great detail included six different Phase III trials, three of them multinational studies. Among the participating sites were three in the USA. The filing, which covered more than 55 000 women who had accepted NORPLANT, filled more than 56 volumes and took several years to complete. Harold

Nash, a senior scientist, and Irving Sivin, a senior associate and biostatistician, led the team preparing the New Drug Application filing. Review and approval by the FDA usually takes from 18 to 30 months — assuming that all goes well and no further information is required. Approval by the FDA is expected in 1990.

Selecting the manufacturer

From its past experience in introducing IUDs, the Council had learned that too many licensees complicate a program and make it more difficult to coordinate training and information. There were eight licensees for the Copper-T IUDs; there would be only one for NORPLANT. What was needed was a company with high standards that would collaborate with the Council in ensuring a reliable supply and an orderly introduction.

When the Council looked for a pharmaceutical manufacturer to produce the limited number of implants needed for the international clinical trials scheduled to begin in 1975, Leiras Medica, Finland's second largest pharmaceutical house, was one of several firms considered. Leiras was selected because it met these criteria, and because it already was involved in worldwide distribution of the Council's Copper-T 200 IUD as well as in the manufacture of oral contraceptives containing levonorgestrel.

When the time came for full-scale introduction of NORPLANT several years later, Leiras expressed interest in continuing the implant manufacture. The Council agreed because it was satisfied both with the company's performance and its attitude. The licensing agreement between the Population Council and Leiras was designed to promote the availability of NORPLANT in developing countries, in addition to the developed countries where Leiras would actively pursue registration and distribution. Wyeth-Ayerst Laboratories is licenced by the Council to distribute NORPLANT in the USA and Canada.

The Council realized that it needed the experience of a private-sector company like Leiras, with the capacity to scale-up manufacturing and production for worldwide distribution. Like most pharmaceutical companies, Leiras had little experience in the Third World but, because the Council had worked extensively in developing countries, the two organizations' strengths would complement each other. From the beginning, they worked closely together in introducing NORPLANT.

History of developing NORPLANT implants

1966 Research and development program begins in the laboratories of the Population Council's Center for Biomedical Research.

1968 First clinical experience with a progestin released from silicone rubber capsules is reported in Santiago, Chile.

1974 Six-capsule Silastic drug-delivery system is developed. First clinical studies begin in Chile.

1975 Multinational Phase III trial is initiated in six countries: Brazil, Chile, Denmark, the Dominican Republic, Finland, and Jamaica. Clinical pharmacology study begins in the USA. Trial is monitored by the Population Council's ICCR.

1980–1982 Preintroduction trials begin in Colombia, Ecuador, Egypt, India, Indonesia, Sweden, and Thailand, and Phase II/III studies begin in the USA.

1982 Comparative trials of the NORPLANT six-capsule and NORPLANT-2 two-rod systems begin in Chile, the Dominican Republic, Finland, Sweden, and the USA.

1983 Leiras Pharmaceuticals of Turku, Finland, is licenced to manufacture and distribute NORPLANT implants. Finland becomes the first country to give regulatory approval to NORPLANT capsules.

1984 WHO evaluates the NORPLANT method in response to a request for a technical evaluation by the UNFPA. WHO concludes that NORPLANT implants are an "effective and reversible long-term method of fertility regulation ... particularly advantageous to women who wish an extended period of contraceptive protection."

1984–1985 Preintroduction trials begin in Bangladesh, China, Ghana, Haiti, Kenya, Nepal, Nigeria, the Philippines, Singapore, Sri Lanka, and Zambia.

1985 Sweden becomes the second country to approve marketing of NORPLANT capsules. The International Planned Parenthood Federation (IPPF) includes NORPLANT on the commodities list made available to its affiliates.

1986 NORPLANT capsules are approved by the Dominican Republic, Ecuador, Indonesia, and Thailand.

1987 NORPLANT capsules are approved by China, Colombia, Peru, and Venezuela. Preintroduction evaluations are under way in Bulgaria, El Salvador, the German Federal Republic, Malaysia, Mexico, Peru, Senegal, South Korea, Taiwan (China), Tunisia, USSR, and Venezuela.

1988 Chile and Sri Lanka approve NORPLANT capsules. Application is made to the US Food and Drug Administration for approval of the six-capsule method.

1989 Kenya approves distribution of NORPLANT. By year's end, more than 55 000 volunteers in 44 countries have accepted NORPLANT in clinical or preintroduction trials.

1990 US Food and Drug Administration approval is expected.

Part II
Introducing NORPLANT

Plans, priorities, and partners

With research and development of NORPLANT essentially complete, the Population Council wanted to ensure that the new contraceptive would be introduced in an accurate, balanced, and culturally sensitive way.

Past experiences with the Lippes Loop and the Copper-T 200 had demonstrated the dangers of over-zealous promotion of a device without provision of adequate information. The importance of those lessons was emphasized by Bernard Berelson, then President of the Council, in 1966.

He related how women who lacked sufficient information tended to discontinue using a new contraceptive on encountering even minor difficulties and to encourage other women to do likewise. "In the first flush of enthusiasm about a method that was both new and loaded with promise, too much attention was given to speeding the work, and too little attention paid to informing women about the difficulties they might expect in the first 2 months of wearing an IUD," he said.

"The *quality of service* is of critical importance when a new and unfamiliar method is being introduced. In short, important as it is to have a satisfactory method, it is equally

Woman in Brazilian clinic shows her implants to friends.

important that women be given a real understanding of what they can expect."

Although the Council, other nongovernmental agencies, and government family-planning programs had heeded the lessons from the early IUD experience, no nonprofit organization had ever attempted to introduce a new contraceptive in a comprehensive way, with attention to user concerns, provision of information, and training.

In 1982, as the introduction of NORPLANT was being considered, the Council formulated a policy to encourage a comprehensive, integrated, long-term plan for systematic worldwide introduction of Council-developed contraceptives. The goal was to attain the widest possible distribution and use for the Council's contraceptives, while ensuring high standards of quality control, appropriate use, information dissemination, and clinical procedure. The policy was approved by the Council's Board of Trustees before FDA approval for marketing the Copper-T 380A IUD and as the introduction of NORPLANT was being contemplated.

Responsibility for introducing both these new contraceptives fell to the Programs Division, headed by the Council's Vice-President, Dr George Brown, a public-health physician and a former Director of IDRC's Health Sciences Division. Although the staff of the Programs Division had experience in providing technical assistance in developing countries, it had never before introduced a new contraceptive for marketing and distribution. Now, they had to determine, for example, when development ended and introduction began. They agreed that, although research on the method would continue, the transition would be triggered when a product was available for marketing in the country of manufacture.

They also had to recognize and deal with the unavoidable fact that decisions already made during the research and development phase of NORPLANT created ripple effects that influenced many of the decisions in the introduction phase. For example, the choice of an implant that did not disintegrate in the woman's arm made it possible for the woman to have the implant removed whenever she wished for whatever reason. That choice created an imperative to provide ready access to removal facilities for all NORPLANT users: this, in turn, raised many logistical issues, such as the need to train health workers in insertion and removal techniques, and to sensitize them to women's concerns about the method. The Council established international training centres for NORPLANT

providers, commissioned the writing and production of information materials for different audiences, and determined that it would conduct a large series of carefully planned, monitored, and supported preintroduction trials to provide in-country data and experience for regulatory filings.

Building on staff experience in the developing world and borrowing from skills honed in the private pharmaceutical industry, the Programs Division sought new ways — and people — to take that experience into the nonprofit sector where sales would not be the main consideration.

Forrest Greenslade, a biochemist with many years' experience in the pharmaceutical industry, joined the Council in 1982. He helped to evolve an integrated plan for introducing a contraceptive through the nonprofit sector. The plan reflected consultations with scientists in developing countries and colleagues in other international agencies as well as numerous interdivisional meetings within the Council.

George Brown recalls, "We had to think through what we could do and how far we could go as a nonprofit organization, in collaboration with a private pharmaceutical company and with the broad network of developing country governments, institutions, donor agencies, and other technical agencies we needed to work with. Although we had indeed achieved a strategy, it was by no means clear that what we had charted out would actually work."

The strategic plan

The strategic plan is a detailed and complex document. In addition to recognizing the importance of collaboration between the public and private sectors, it spells out the

Forrest Greenslade (centre) at a meeting of the NORPLANT *collaborators.*

numerous steps that must be taken to integrate NORPLANT into a country's family-planning network.

For example, one section covers manufacturing, obtaining local regulatory approvals, and arranging for marketing and distribution — basically the responsibilities of Leiras Pharmaceuticals as the Council's licensee for NORPLANT. Leiras is also concerned with distributing the implants both through public programs and commercial channels.

A second section derives from the ICCR research and development efforts. It includes establishing international training centres to develop clinical expertise, training of clinicians and counselors, and conducting preintroduction field trials. As in-country programs prepare for widespread use of the implants, guidelines for incorporating NORPLANT into family-planning services and a detailed training curriculum are prepared.

A third section covers providing information about the method to different groups — ministry of health officials, women's groups, and medical professionals — and developing special information materials for users and their families and for health-care providers.

Another of the plan's goals was to coordinate the large collaborative effort of scientists, donor agencies, international organizations, and family-planning programs. As the program matured and NORPLANT was approved in several countries, detailed strategies were developed to assist family-planning programs in managing expanded activities, training, and supervision, and in obtaining supplies.

"The larger the distribution becomes, the more difficult it will be for the Council to monitor or influence how NORPLANT is dispensed. It is vital for the Council to follow through with the parts of the strategic plan that deal with utilization — in-country training of health-care workers, gathering of data, and paying attention to the user's needs and perspectives."
Forrest Greenslade

An evolving strategy

The strategic plan has evolved as the NORPLANT introduction program itself has evolved, changing to meet field conditions in developing countries, as the following examples illustrate.

- Counseling always was an important part of the program. It received even higher priority when research demonstrated that proper counseling and information increased user satisfaction.
- The discovery that women in some countries were encountering obstacles to having the implants removed forced the team to develop new approaches to ensure that access to removal on request was guaranteed.

"Some remember the NORPLANT development as one smooth continuum, but it was never that sharp and clear."
Wayne Bardin

- When data from one Asian country showed that an unusually high number of women had infections at the insertion site, Council field staff and country investigators retrained some of the providers in maintaining aseptic conditions.

In short, it is a measure of the plan's validity that it has adapted so well to handling unexpected problems.

The transition from development to introduction to incorporation into family-planning programs has not been as smooth as expected, for two reasons that were not foreseen when the strategic plan was developed. One circumstance was the delay in filing the New Drug Application with the FDA. This delay meant that USAID could not distribute supplies of NORPLANT even when requested by family-planning programs, because USAID can only distribute products that have FDA approval for marketing. As a result, country programs that were ready to begin widespread use of the implants had to scale down their efforts.

Another event that upset the introduction timetable was the setback with NORPLANT-2, the two-rod version that had been expected to be the most widely used method. Although most countries had experience with both versions of NORPLANT, a few programs had opted to conduct clinical trials with only the rods or to delay introduction until the rods were available.

Organizing a management infrastructure

The introduction team assembled by the Programs Division includes specialists in maternal and child health care, women's advocacy, information and educational materials, and social science research. The team provides a central management infrastructure for the day-to-day coordination, planning, prodding, and trouble-shooting that keeps the introduction program on track. It maintains contacts with the pharmaceutical manufacturer, collaborating agencies, consultants, and donors, as well as overseeing the development and conduct of preintroduction trials, training, user research, and information materials.

Two in-house advisory groups support the program. The NORPLANT Working Group comprises five management and public-health experts from the Programs Division and four scientists from the Center for Biomedical Research. It focuses on issues related to the conduct of preintroduction

trials, data collection, interaction with the manufacturer, scientific and medical questions, and technology transfer. The NORPLANT User Perspective Committee draws members from both the Programs and Research divisions. It works on issues relating to women's roles and status in developing countries.

The Council's Office of Communications works with both committees to produce and coordinate prototype materials and to disseminate information. The field staff play a critical role in establishing and maintaining relations with institutions and ministries in the developing world; three full-time medical associates — in Asia, Latin America, and sub-Saharan Africa — visit clinics and programs regularly, monitoring the trials, consulting on problems, and encouraging the research and training efforts.

A network of collaborators

The Council has been able to expand the reach of its own staff and resources by forging collaborative relationships with other organizations. Several collaborating organizations became part of the introduction team, helping to supervise preintroduction trials, prepare user and training materials, and establish a worldwide data base. Three organizations in particular have played major roles.

- Family Health International (FHI), one of the largest international scientific networks for evaluating new contraceptive techniques, manages and analyzes large-scale NORPLANT preintroduction trials in the Third World.
- Program for Appropriate Technology in Health (PATH), dedicated to improving the effectiveness, safety, availability, and acceptance of health products in developing countries, assists in developing prototype information materials about NORPLANT for users and health workers, and coordinates testing of the training curriculum.
- Association for Voluntary Surgical Contraception (AVSC) aids the Council in setting up training programs for NORPLANT clinical procedures.

Leiras Pharmaceuticals is also a key collaborator, working closely with the Council, obtaining country registrations, and establishing distribution networks; Wyeth-Ayerst, which holds the licence from the Council for

An international workshop at FHI headquarters (left to right, Maria Margarita Diaz from Brazil, Albert Collison from Ghana, Sandor Balogh of FHI, and Emmanuel Dow from Ghana).

the US and Canadian distribution, has also been an important contributor.

Council staff also established links with three international organizations whose cooperation was crucial — WHO, UNFPA, and IPPF. A major boost to the NORPLANT program was an evaluation of the method by WHO's Special Programme of Research, Development, and Research Training in Human Reproduction. At the request of UNFPA, WHO reviewed clinical and preclinical information on the new contraceptive, and concluded early in 1984 that: "NORPLANT provides an effective and reversible long-term method of fertility regulation. It is considered suitable for use in family-planning programmes, along with other currently available contraceptive preparations and devices, since it provides an important option for women desiring long-term contraception."

Throughout the introduction program, WHO has maintained a close relationship with the Council, sharing information on health-related issues and assisting in the preparation of a comprehensive publication to guide countries seeking to incorporate NORPLANT into their family-planning programs. WHO is also managing a preintroduction evaluation of NORPLANT in Tunisia, and is collaborating with the Council and FHI in a long-term surveillance to identify any unexpected adverse experiences with the method. In the past, adverse conditions have tended to be noted haphazardly, often years after a product is introduced.

Since 1984, UNFPA has provided both financial support and encouragement for activities central to the introduction of NORPLANT. UNFPA has also purchased supplies of implants for preintroduction evaluations in developing countries. This is an important contribution because, until NORPLANT receives FDA approval, USAID can provide implants for research purposes only. Once NORPLANT is approved, USAID, which has played a significant role in the research and development program, is expected to become a major distributor of the implants. USAID has also contributed to country-level research projects, and has provided both financial and conceptual support to the management of the program.

IPPF, whose affiliates carry out family-planning programs in 120 countries, was briefed regularly on the method during the years of development. In 1985, IPPF requested detailed information to see if NORPLANT should be made available to its affiliates. After a presentation by the Council to the Federation's International Medical Advisory Panel, IPPF agreed to include NORPLANT on its commodities list, thereby establishing a mechanism for worldwide distribution of the implants to its affiliates.

IPPF concurred with the Council's approach to country use. This stipulates that, before the organization would ship NORPLANT to any affiliate, the method must have been approved for distribution by the regulatory authorities in the country involved, and a sufficient number of health workers must have been formally trained in insertion, removal, and counseling techniques.

Raising money

By 1982, the Council had already spent more than 10 million USD on NORPLANT research and development. Its principal donors for this phase of the program had been various US foundations, USAID, UNFPA, and IDRC. The introduction program would cost at least 6 million USD in the first 3 years, with funding from IDRC, the Hewlett Foundation, USAID, and UNFPA.

For a nonprofit organization such as the Council, raising money poses challenges. A highly integrated program like the NORPLANT introduction requires funding not only for developing-country projects but also for Council managerial and support staff. Each donor agency has different priorities; each wants to see its limited resources directed to

developing countries or persons. Fortunately, through an intensive program of personal contacts and meetings to convince international donor agencies of the importance of an organized introduction program, the Council was able to obtain funding for its management infrastructure as well as for specific projects.

Although NORPLANT is easy to insert and remove, these operations should not be performed by untrained medical personnel. Only through hands-on training can a physician or paramedic appreciate the delicacy of the technique, the correct manipulation of the long needle used in inserting the capsules, and the potential problems in removal when implants are placed too deeply. Insertion and removal of NORPLANT are performed under local anesthetic; insertion takes 10–15 minutes, routine removal a little longer.

Special centres established to train clinicians in NORPLANT insertion and removal were based on the expertise developed during the ICCR's clinical trials with the techniques. Several leading medical institutions in countries that participated in the early ICCR trials were selected to serve as international training centres. The Raden Saleh Clinic in Jakarta, Indonesia, and the PROFAMILIA clinic in Santo Domingo, the Dominican Republic, have trained physicians from Asia, Latin America, and sub-Saharan Africa; the clinic at Assiut Hospital in Assiut, Egypt, which became operational in 1989, will train clinicians from North Africa. A clinic in Santiago, Chile, the Instituto Chileno de Medicina Reproductiva, served as a training centre for the

The texture of the "training arm" developed by PIACT closely resembles that of skin and muscle tissue.

Francisco Alvarez-Sanchez, head of the NORPLANT international training centre in the Dominican Republic uses the "training arm" to teach clinicians how to use the trocar.

early clinical trials. Leiras also has trained physicians from several countries at its facilities in Turku, Finland.

Physicians from countries wishing to introduce NORPLANT attend 3-day training sessions at the international centres where they practice insertion and removal and attend sessions on counseling users, the importance of aseptic technique, problem management, data collection, and record keeping. The trainees are taught the risks and benefits of all available contraceptives so as to view NORPLANT in a balanced way. Through slide lectures, videocasettes, and handbooks, the clinicians are instructed in all aspects of the technique and associated service-delivery questions.

When the clinicians return to their countries, they initiate trials in their own clinics and develop the training capacity for eventual widespread use. So far, the centres have trained only physicians, but some country programs are training paramedics as well. Research in Indonesia demonstrated that nurses and nurse-midwives perform the procedures as well and as quickly as physicians.

Preintroduction trials

The early extensive research on and development of NORPLANT was carried out in experienced clinical research institutions. These studies were essential to learn about the method's characteristics and acceptability to women.

The preintroduction trials, however, offered an excellent means for countries to prepare for the introduction of NORPLANT. Unlike clinical trials, which are usually small, carefully controlled, and conducted in university hospital clinics, preintroduction evaluations are closer to actual conditions in the field.

The appropriate regulatory agency in each country (usually the ministry of health) must give written approval before a local family-planning organization can conduct a preintroduction trial for a new method. Included with the application is a protocol for introduction, specially tailored to the country's program, that lists the purpose of the trial, the number of women to be enrolled, and other conditions to be followed. Council staff work with the coordinating organizations to organize the trials and standardize the records so that the data can be used for regulatory filings.

These are larger-scale trials: they usually include from several hundred to a few thousand women although as many

as 10 000 users at up to 10 locations have participated in some studies. The trials are held in a variety of settings, ranging from public hospitals and university teaching centres to health clinics. One institution in each country is designated as the study coordinating centre. Two staff members — a physician medical advisor and a nurse-midwife — act as "trouble shooters," identifying and addressing problems experienced by any of the clinics in the study. They are also responsible for organizing such activities as data collection, medical and clinical procedures, and counseling.

The trials provide training for the core group of health workers who will administer the method, counsel users, and prepare information materials; they enable officials to assess potential user demand for NORPLANT and to integrate the method into the health-care delivery system. By the end of 1989, 44 countries and more than 55 000 volunteers had participated in clinical or preintroduction trials conducted by the Council, FHI, WHO, and Leiras Pharmaceuticals. Of these countries, 13 are in the Americas, 8 in Europe, 7 in sub-Saharan Africa, 3 in North Africa and the Middle East, and 13 in Asia.

The trials also provide insights into the acceptability of NORPLANT to women of various cultures and religions. They frequently reveal unexpected needs of users or that additional training, counseling, and services are required. The trials enable collaborating national institutions to determine the niche that NORPLANT might fill in their family-planning programs, and the demands the method would place on clinic facilities and staff. They help Council staff reach a better understanding of the broader program implications of the contraceptive, which is not always possible during the early phases of research.

Countries that have participated in trials

Bahamas, Bangladesh, Belgium, Brazil, Bulgaria, Chile, China, Colombia, Denmark, the Dominican Republic, Ecuador, Egypt, El Salvador, Finland, France, German Federal Republic, Ghana, Haiti, India, Indonesia, Israel, Jamaica, Kenya, Malaysia, Mexico, Nepal, Nigeria, Pakistan, Peru, the Philippines, Rwanda, Senegal, Singapore, South Korea, Sri Lanka, Sweden, Taiwan (China), Thailand, Tunisia, USA, USSR, Venezuela, Zaire, and Zambia.

Worldwide data base

Most preintroduction trials include research studies that expand knowledge about the characteristics of the method. Many of these studies have been published, providing a continually growing base of information about the use and effects of NORPLANT implants.

One objective of the preintroduction trials is to document the results of local and international experience with the method so that the data can be submitted to regulatory agencies. To achieve this objective, the Council and collaborating agencies and clinics have established the

"To my knowledge, this is the first time a data base of this type has been set up for the worldwide introduction of a contraceptive method. We are very excited about this project and hope that it becomes a valuable research tool."
Nestor Anderson

first worldwide data base for the introduction of a new contraceptive, with data on more than 50 000 users of NORPLANT. Records are kept of such significant events as pregnancies, continuation rates, and reasons for removal.

Using standardized record forms, clinics send copies of each case record to national coordinating centres, which then forward the data on computer diskette either to regional centres or directly to FHI in the USA, where the data are stored and analyzed on a mainframe computer. Summarized data from each clinic are sent to the appropriate investigator. The data from that particular clinic are compared with data from all other sites in the same region, the country, and the world. A key component is a regional data base in Campinas, Brazil, that captures information from preintroduction trials throughout Latin America.

Acceptance and rejection

The NORPLANT introduction strategy emphasizes that counseling of actual and potential users should be done in a nonpromotional way, giving balanced information on all aspects of the method. Counselors are encouraged to compare NORPLANT with all other available methods to assist each woman in choosing the contraceptive best suited to her needs and lifestyle.

Counseling techniques are taught at the training centres and through the in-country programs. The trainers point out that good counseling dispels rumours and helps women anticipate side effects such as the irregular bleeding they may experience, particularly during the 1st year of NORPLANT use. More women discontinue using the implants because of bleeding irregularities than for any other reason.

Health workers in the NORPLANT program must learn to counsel potential and current users on a wide range of real and imagined problems. These include worries about whether the method will cause discomfort, or interfere with their daily activities or their sexual relations, and about such factors as possible weight changes, skin problems, and headaches.

The program emphasizes that a woman's right to discontinue use of the method is just as important as her right to choose a particular contraceptive. Obstacles to removal — for example, if a woman must wait hours at the clinic, or if she must return days or weeks later because staff

members are not available — may lead her to seek out untrained providers. In one case, a woman went to a dentist to have the capsules removed!

Because the implants provide 5 years of protection against pregnancy and relatively few women request removal in the 1st year, programs must run several years before there are enough users to provide much removal training. By 1983, however, when the implants were ready for introduction, sufficient numbers of women were using the method to provide opportunities for training in removal as well as in insertion.

Clinicians have been known to be reticent about removing implants for various reasons. One is that they may be concerned about their own lack of practice in performing removals: but the more practice they get, the more willing they will be to remove implants. During clinical trials, investigators may be concerned that scientific data will be rendered incomplete if the women do not keep the implants. These concerns are unfounded because clinical trials are designed to measure acceptability as well as effectiveness and side effects. High continuation rates reflect user satisfaction with the method only when women have adequate access to removal.

Researching the users and the program

Although the scientific data reflect continuation or discontinuation with NORPLANT, it is just as important to determine user satisfaction with the method and with the system that delivers it. To do so, the NORPLANT introduction program also emphasizes research on the needs of the users and the program.

The feedback provided by users through surveys, focus group discussions, and in-depth interviews has already helped programs strengthen their counseling and other delivery services, and has been incorporated into information materials. With these probe studies as background, in 1987, the Council and its collaborators launched a program of research on the determinants of user satisfaction with the method and the service-delivery system. The program will include thousands of NORPLANT users and former users in Southeast Asia, sub-Saharan Africa, and Latin America. The results of this program will be used to guide family-planning managers, health-care providers, and managers of training programs. With a focus on service

delivery, the research will help providers improve their counseling, information, and training strategies.

Communicating about NORPLANT

Good communication is an important and frequently undervalued element of the introduction process. Misinformation and rumours can seriously hamper a program to introduce a contraceptive. Accurate and balanced information can be presented in various ways, such as meetings, media interviews, and publications.

In countries where approval is required for NORPLANT use, ministry of health and regulatory officials receive regular reports and briefings by project investigators. This can be especially important when a new administration takes office: politicians sometimes question the decisions of their predecessors and a lack of information may leave a contraceptive program vulnerable to political controversy.

Opinion leaders such as consumers' and women's health-care advocates can also have great positive or negative effects on a contraceptive-introduction program. In October 1986, the Council and the International Women's Health Coalition organized a meeting with scientists, service providers, and family-planning proponents at the Council to discuss questions on contraceptive development and introduction. The meeting — like similar efforts in different countries and regions — was intended to forge channels of understanding between women's health advocates and service providers.

"Don't underestimate the importance of keeping open lines of communication: not only with friends of the technology, but also its detractors. Only through open dialogue can you minimize misunderstanding. An introduction program needs honest, open, aggressive communication to decrease the amount of misinformation around."
Forrest Greenslade

Another example of information-sharing came in the summer of 1987 when the Council learned that the elastomer used in the NORPLANT-2 rods was no longer going to be manufactured. The biomedical scientists and the introduction team conferred, evaluated the options, and decided on a course of action: arrange for an independent scientific evaluation of the elastomer; hold a meeting immediately with all the NORPLANT investigators to inform them of developments and obtain their advice; and conduct similar meetings with collaborators, donor agencies, and women's health groups.

This pattern of open discussion continued after the investigators returned to their countries. The Council sent detailed memoranda outlining the decisions made. Staff prepared an easy-to-understand explanation that counselors or clinicians could use to inform NORPLANT users of the

situation. The November 1987 issue of the NORPLANT newsletter, *NORPLANT Worldwide*, also featured an explanation of the situation. By acting promptly and providing information to all concerned groups, the Council was able to defuse what could have become a very troublesome situation.

A balanced information program provides material for a variety of audiences. These include the users themselves, health professionals (particularly in clinics and hospitals where NORPLANT is or might be offered), colleagues in population-related organizations, actual and potential donor agencies, women's health groups, decision-makers and opinion leaders in developing countries, and government officials in countries where applications could be made for regulatory approvals.

Some of the material is prepared by the Council and its collaborators as prototypes. These are used by those involved in family-planning programs in individual countries

Surveying the users

The introduction of NORPLANT in more than two dozen developing countries with various health-delivery systems, unequal levels of development and literacy, and differences in cultural and religious preferences has provided researchers with abundant opportunities to plumb attitudes and preferences about family-planning methods. Over 18 country programs are involved in user and program research dealing with attitudes toward the method, ways to improve service delivery, clinic management, and counseling. The following are a few examples.

- Using focus-group studies, a research method borrowed from commercial marketing, PATH has collaborated with institutions in the Dominican Republic, Egypt, Indonesia, and Thailand to conduct in-depth discussions among NORPLANT users, former users, and providers.
- A four-country study undertaken by FHI involved about 2 000 potential users at 10 family-planning clinics in Bangladesh, Haiti, Nepal, and Nigeria. The survey identified potential sociocultural obstacles to NORPLANT acceptance such as concerns about menstrual irregularities and husbands' disapproval.
- A study of women using NORPLANT in a clinical trial in the USA sought to evaluate acceptability, attitudes toward insertion and removal, and whether women would use NORPLANT again or would try another method.
- In Bangladesh, researchers conducted intervention counseling of husbands of NORPLANT users to see if such counseling affected continuation rates.
- Family-planning clinics have to develop strategies to remind women to return after 5 years to have their implants removed. A study in Brazil looks at which women return without being reminded and ways to remind the other users.
- A four-city study in Egypt seeks to improve future counseling about NORPLANT through increased understanding of attitudes and beliefs about contraception.

Testing the Spanish-language users' brochure.

to prepare their own information materials to inform and attract accepters, or to train clinicians and counselors.

Leiras has prepared information materials and audiovisual training aids in both English and Spanish, including an instruction brochure and training videotapes for clinicians on techniques to insert and remove NORPLANT. The *Guide to Effective Counseling*, published in English, French, and Spanish, was prepared by Council staff, PATH, and Leiras. The newsletter is published regularly and widely distributed. Other Council publications include a scientific monograph summarizing the data about NORPLANT, a handbook for clinicians detailing insertion and removal procedures, an information guide for decision-makers, and fact sheets comparing family-planning methods and giving details about aseptic procedures for insertion and removal. (A short bibliography is included at the end of this book.) Council staff also worked with WHO to prepare a guide for incorporating NORPLANT into country programs. The guide includes medical information about the method, instructions for insertion and removal, advice on how to determine supply and personnel needs, and a checklist for counselors.

In an attempt to overcome some of the problems created by illiteracy and differing cultural perspectives, special brochures have been prepared for users in different regions and of different cultures. For the introduction program, PATH has collaborated with local experts and artists to produce prototype brochures that contain drawings — even comic strips — augmented by a line or two of simple text in the local language. The counselor reads

the booklet to the user, and the pictures help reinforce the message in later months or years.

Council staff and others involved in the introduction program also present research results to scientific peers on a regular basis. International meetings, such as the World Congress on Fertility and Sterility, highlight the latest research data on NORPLANT. The Council sponsors information briefings for various groups and maintains a vigorous public-information program.

Incorporating NORPLANT into country programs

Before a new drug can be used in a country — for trials or widespread incorporation into family-planning programs — it must have regulatory approval. Leiras Pharmaceuticals is responsible for obtaining regulatory approvals for NORPLANT around the world, except in the USA, where this function is assumed by the Council. Before a new drug can even be exported, however, it must first be approved in the country in which it is manufactured. Leiras took the first step in the fall of 1980 when it filed for registration of NORPLANT capsules in Finland. Regulatory approval there was granted in November 1983.

By the end of 1989, NORPLANT was approved for marketing in 13 countries — in order of approval, Finland, Sweden, Indonesia, Thailand, Ecuador, the Dominican Republic, Colombia, Peru, China, Venezuela, Sri Lanka, Chile, and Kenya — and trials were being conducted in 44 countries. Leiras' marketing plan assumes that over the next few years applications for approval will have been filed in about 40 countries.

The Population Council has handled the necessary regulatory filings before the FDA, including the 1974 Investigational New Drug application permitting clinical

John Gill, The Population Council's senior medical associate in Bangkok and former Director of IDRC's Health Sciences Division, with Joanne Spicehandler, until recently manager of the NORPLANT *introduction program.*

studies and the August 1988 New Drug Application for marketing approval of NORPLANT capsules. Approval in the USA is expected in 1990. The US clinical studies were conducted at hospitals in Los Angeles and San Francisco, California, and in New Brunswick, New Jersey. Wyeth-Ayerst Laboratories will be the US marketing agent.

Registering new contraceptive methods requires Leiras to be aware of local laws and customs, and to stay in contact with authorities in ministries of health at all stages of the introduction, approval, and distribution process, particularly when the drug is under review. Unlike the fairly uniform requirements that now exist in the developed world, registration requirements in the developing world differ widely from country to country. Some require clinical trials, others accept the international file submitted by Leiras of studies conducted in other countries. Some permit applications to be made while trials are still in progress, while others do not. In the USA, the FDA requires submission of all relevant data, which explains why submissions to this agency often fill scores of folders.

Another of Leiras' prime responsibilities is to establish the marketing and distribution networks in developed and developing countries alike. As each country approves the method, Leiras arranges the necessary distribution links.

Once the method is registered, Leiras, together with the local distributor, assumes overall responsibility for the way the drug is marketed, distributed, promoted, and sold. In most countries, pharmaceutical imports that affect people's health are generally subject to close governmental scrutiny. Laws in most developing countries require that distributors be locally licenced pharmaceutical houses that can take responsibility for the drugs they handle.

Going slowly with incorporation

Regulatory approval is only the first step in incorporating a new contraceptive into existing national family-planning programs. Although the health-delivery system may vary from one country to another, experience has taught that it is best for providers initially to incorporate NORPLANT into family-planning programs on a small scale so that any problems can be overcome while they are still manageable.

Just as there is a strategic worldwide plan for introducing NORPLANT, so also there is a list of all the

Using a battery-powered lamp, J.K.G. Mati inserts NORPLANT *capsules in the arm of a volunteer in a rural clinic in Kenya.*

recommended steps to be taken before the method attains countrywide distribution. It is at this stage that Council staff and their collaborators hand over responsibility to the operators of local programs and to local scientists and policymakers. Throughout the incorporation process, however, the Council and collaborating organizations consult with country-program officials, providing technical assistance when required and requested.

Supervision of services, easier to provide when NORPLANT is limited to smaller numbers of women in clinical trials, is even more important in an expanded program. Experience gained in the trials can serve to alert providers to possible weaknesses that may occur in the introduction of the program. In Kenya, for example, Council staff working with local health officials and family-planning experts were aware of special problems in rural clinics that had no electricity or running water. Staff at Kenyatta National Hospital in Nairobi overcame the problem by first sterilizing the NORPLANT equipment, then wrapping it in special disposable towels, which were packaged along with the sterile packets of NORPLANT capsules and delivered to the rural clinics. The trial project at six rural clinics involved 300 volunteers with not one case of infection reported. The experience will serve as a model not just for Kenya but also for other sub-Saharan African countries.

As country programs seek to introduce NORPLANT into their existing delivery systems, a network of trained professionals can be called upon for technical assistance and medical back-up. Drawing on experience gained in countries where the program has been introduced, a core of

physicians, nurses, social scientists, and the Council's regional staff stands ready to advise on program training and medical requirements, and to provide information. Individuals from developing country institutions that have experience with NORPLANT can also be called upon to serve as consultants.

Sensitive counseling "is possibly the most important factor in maintaining NORPLANT's high continuation rates." *John Gill*

All the necessary medical and support services should be firmly in place before large numbers of women are accepted. Incorporating NORPLANT into existing programs requires trained clinicians and counselors who can use a locally adapted training curriculum to train other providers in the method; educational and information materials in local languages; record forms and procedures to monitor and evaluate services; supply and distribution systems; and adequate funding to cover the heavy initial costs for a method that is provider dependent.

Training sessions alert program managers to plan ahead for service provision. A caseload of a certain number of accepters, for example, requires sufficient trained staff and ample sets of implants in the clinic. An established and posted clinic schedule should inform both staff and clinic users of the days and times when NORPLANT can be inserted and — just as important — when the implants can be removed.

Reminding women who have kept their implants for 5 years that it is time to return for removal poses an even more challenging problem for clinic management. The most productive ways to communicate instructions to accepters may vary with the country, region, culture, and available media. Although the insertion date and clinic location are included in the NORPLANT information brochures given to users, not every user is literate. A reminder by mail or telephone may not always be possible or practical, and in highly mobile societies even tracing women is not easy. Under such conditions, clinics have to devise innovative ways to convey messages about removals to NORPLANT users.

Each country must also decide how best to organize its training program. The "pyramidal" approach used with large numbers of providers in China, Indonesia, and Thailand can serve as a model for other programs using this approach. Only a few physicians were trained initially at the Raden Saleh Clinic in Indonesia. These staff then trained the next level of health workers, who, in turn, trained personnel from other hospitals and health centres in their own and other provinces.

In Indonesia, where more than 250 000 sets of NORPLANT have been distributed, the program has depended on nurses and midwives as well as on physicians to provide services. A study at Raden Saleh demonstrated that nurses and midwives were able to perform the insertion and removal procedures as well and as quickly as physicians. For the Chinese program, four physicians from four provincial centres were trained initially; they trained enough colleagues to enable expansion of the clinical trial to eight additional centres with satellite clinics, for a total of 23 clinics. Some 12 000 women accepted NORPLANT in the Chinese trial. In Thailand, where about 30 000 women use the implants, 700 physicians have been trained in NORPLANT procedures at 12 regional centres. About 300 nurse-midwives from 11 provinces have been trained in counseling techniques.

Prototype training curriculum

To prepare for expansion of the method beyond the preintroduction trials, a 5-day in-country training course was developed by an interagency task force of the Council, PATH, FHI, and AVSC. Although the courses developed by the international training centres are appropriate for use in small trials conducted at quality clinics by well-trained physicians, country training programs have further needs. Nurses, nurse-midwives, other paramedics, counselors, social workers, and other clinic staff have to be informed about NORPLANT in addition to physicians. The goal is to make the service provided as acceptable and consistent as possible. When NORPLANT is registered in individual countries, medical and nursing schools are encouraged to offer courses on the method.

Sriani Basnayake, Medical Director of the Family Planning Association of Sri Lanka, with an accepter during the NORPLANT procedure.

The comprehensive curriculum was tested in January 1989 by a training team at the university teaching hospital in Ibadan, Nigeria, assisted by staff from AVSC and PATH — NORPLANT was first introduced in Nigeria in 1985 in trials monitored by FHI. The curriculum will be tested in Bangladesh in March 1990 and in a program in Latin America. The final version, with detailed instructions and audiovisual aids, will then be available in different languages for adaptation by country programs.

Equally divided between theory and practice, the curriculum provides each trainee with a thorough knowledge of NORPLANT, the management skills needed to run clinics, and the ability to insert and remove implants and counsel

women. Time also is given to problem solving and role playing.

Postmarketing surveillance study

To learn about any possible rare events associated with long-term NORPLANT use, a postmarketing surveillance program has been established by WHO, FHI, and the Council. This joint study will follow some 8 000 NORPLANT users and controls for 5 years. It is the first long-term internationally coordinated surveillance of a contraceptive's effectiveness, side effects, and continuation rates.

The NORPLANT users will be followed for 5 years, even if they discontinue using the implants. The study seeks to learn what happens to women even after they switch to another method or become pregnant. It focuses on rare events of public-health importance, such as hospitalizations and deaths, as well as on any incidence of events not easily recovered from hospital records, such as tubal pregnancies.

The study began in June 1987 with a pilot project in Chile, Sri Lanka, and Thailand involving 450 NORPLANT users and 450 women who did not use implants. A 1-year evaluation meeting was held with the investigators in Bangkok in June 1988 to discuss results, fine-tune the questionnaire, and plan the next stage of the project. The full surveillance project started in the autumn of 1988 at multiple centres in Bangladesh, Chile, China, the Dominican Republic, Indonesia, Sri Lanka, and Thailand.

Maintaining the supply line

The delay in filing for FDA approval of NORPLANT, described earlier, meant that USAID, one of the largest purchasers of contraceptives for the developing world, could only supply implants for research and training studies. USAID is prohibited by law from supplying drugs that have not obtained FDA approval.

The NORPLANT supply line, therefore, was slowed and, although UNFPA and other donors such as the Asian Development Bank have purchased some supplies and provided funds for training and other sources, a shortage of implants may cause some country programs to phase in the introduction of NORPLANT more slowly than they had planned. A few programs may not be able to afford the cost of clinical trials, field trials, and initial training sessions

Cost estimates for contraceptives.

Method	Unit cost (USD)	Duration per unit	Annual cost (USD)	Average use (years)	Adjusted annual cost (USD)
NORPLANT	18.00	5 years	3.60	3–3.9	4.50–6.00
IUD (copper)	0.65	4 years	0.15	2–2.7	0.25–0.30
Oral contraceptives	0.17	1 month	2.21	—	2.40–2.80
Injectable contraceptives	0.80	3 months	3.26	—	3.50–4.00
Diaphragm	3.30	1 year	3.30	—	3.50–4.00
Spermicide (tablets)	1.52	20 uses	7.30	—	8.00–9.00
Condom	0.03	1 use	2.98	—	3.25–3.75

although the actual capsules and trocars are provided by donors or agencies supporting the studies.

When requested, the Council helps process applications to donating agencies and foundations for supplies, training, education, and logistic support. When clinical trials are completed and NORPLANT has been registered, the health ministry or family-planning association has to grapple with budgeting decisions. It must be able to project how many sets of implants it can afford and must determine who will pay for them, the relative importance of the method compared with other contraceptives provided, and what help will be needed from outside resources. For NORPLANT, an additional obstacle arises compared with other methods: it is a 5-year method, so the cost is mostly up front and not spread out as with The Pill and injectables.

The cost of the capsules is difficult to estimate because it depends on so many variables. Under the Council's contract with Leiras, nonprofit programs in developing countries are sold NORPLANT at a reduced price. However, even the manufacturer's price varies, depending on the quantity ordered at one time and the distance the shipment must travel. Some factors are outside the manufacturer's control, such as taxes, changes in the exchange rate of the US dollar versus other currencies, customs duties, distribution costs, service charges of local programs, and so on. By the time NORPLANT has reached outlying family-planning clinics, the cost to the purchaser may have doubled or tripled.

Although it is not possible to project accurately how much a set of NORPLANT implants will cost, or how that cost compares with the cost of other methods, estimates can be made based on large-scale purchases by public-sector donor agencies such as UNFPA in 1988. The table above compares NORPLANT at 18 USD/set with other

contraceptives, accounting for the average duration of use and the duration of the method's effectiveness. The estimates do not include transport to the destination country, import fees, or distribution or service-delivery costs.

In most developing countries, and in some developed countries such as those in Scandinavia, contraceptive purchases are subsidized by the government so that the consumer pays a low price or nothing at all. In private-sector programs, of course, costs are higher, and doctors' fees in developed countries may add 100 USD or more to the cost. In the USA, where both private physicians and public-sector clinics will offer NORPLANT, the price to the consumer undoubtedly will vary widely.

It is Council policy to provide — where feasible and practicable — for the technology for manufacturing NORPLANT to be transferred to local manufacturers. Leiras is equally committed to this program.

Since 1983, the worldwide experience with NORPLANT has been varied and extensive, ranging from countries just beginning to train physicians before preintroduction trials to family-planning programs with many thousands of implant accepters and a sophisticated array of information material. Even after the method is incorporated into a family-planning program, the research continues into aspects of service delivery, acceptability of the method, and long-term use.

Part III
Evaluation and analysis

Lessons learned

Much has been learned from the development and introduction of NORPLANT. The insights gained over the 20 years of the NORPLANT project may provide guidance to another nonprofit agency considering the development or introduction of another new contraceptive — or they may discourage such a venture. In either event, this chapter offers some of those lessons for the benefit of others who may later tread similar paths in search of other new technologies.

The broad outline of the Population Council's NORPLANT program includes research into a new concept, development of a new technology, introduction of the technology to the international health-care community, and incorporation of the method into existing national delivery systems around the world. Specific features make the NORPLANT program unique: emphasis on widespread clinical and preintroduction trials, sensitivity to users' concerns, continued biomedical and social-science research, establishment of international training centres, development of information and education materials, and formation of a worldwide network of professionals knowledgeable about the method.

The Council's experience with NORPLANT shows that the nonprofit sector has the capability to advance the research, development, and introduction of contraceptives — but only through collaboration. Forrest Greenslade, the Council's consultant for contraceptive introduction, points out that "no one institution has all the resources to introduce a contraceptive technology by itself. We have to collaborate with other nonprofit organizations and with the private sector."

Although other new technologies might require different approaches to development and introduction, certain themes from the NORPLANT project might be useful for other organizations that attempt this kind of venture.

Public- and private-sector interaction

NORPLANT research, development, introduction, and incorporation into national family-planning programs would not have been possible without collaboration between

private companies and public institutions and organizations. The following table illustrates this point.

The public sector's contribution to contraceptive and health-care innovation went beyond basic biomedical research. It included mobilizing and coordinating organizational resources required for introduction. These resources included specialists in academic centres, nonprofit organizations, international agencies, and institutions in both developed and developing countries who contributed to the emergence of implant contraception.

The NORPLANT innovation process.

Key step	Resource		
	Population Council	Other public[1]	Private[2]
Research leading to implant contraception			
Basis of progestin-only contraception	•	•	•
Steroid and polymer technologies			•
Laboratory and animal studies of implant concept	•		
Pilot clinical studies of implant concept	•		
Clinical studies to select optimal steroid	•		
Animal safety of levonorgestrel/Silastic	•	•	•
Development of NORPLANT method			
Clinical pharmacology studies	•		
Clinical studies of effectiveness and safety	•		
Dose form development	•		•
Agreement for manufacture and distribution	•		•
Scale-up for manufacture	•		•
Regulatory approval for distribution	•		•
Introduction of NORPLANT			
International training centres	•	•	
Preintroduction clinical trials	•	•	•
User and program research	•	•	
Training and information materials	•	•	•
Guidelines for program use	•	•	
Local regulatory registrations			•
Manufacture, marketing, and distribution			•
Incorporation of NORPLANT into family-planning programs and services			
In-country training programs	•	•	
Adaptation of materials for IE&C[3]		•	
Strengthening infrastructure for service delivery		•	
Procedures for procurement and logistics		•	•
Standards for program evaluation		•	

[1] Academic centres, nonprofit organizations, international agencies, and institutions in developing countries.
[2] Pharmaceutical industry and commercial channels.
[3] Information, education, and communication programs.

Private industry provided the silicone rubber and hormones used by the Council for NORPLANT. Other crucial private sector functions, provided by Leiras Pharmaceuticals, included manufacturing capacity, marketing skills, and distribution channels. None of these roles could be replicated easily by nonprofit organizations.

By working with the pharmaceutical industry, the Council was able to gain access to steroid and polymer components already approved by the regulatory agencies. This resulted in major savings in development costs, and facilitated the scaling-up of the manufacturing process when that time came. An agreement with American Home Products (parent company of Wyeth-Ayerst Laboratories) gave the program access, for purposes of regulatory filings, to the animal safety studies that had been carried out by that company. Replicating the studies would have cost several million dollars and delayed the development process.

Similarly, time and money were saved by FDA rule changes that permitted cross referencing of animal safety studies of another levonorgestrel-containing implant called Capronor. The studies were conducted by Research Triangle Institute under the sponsorship of the US National Institute of Child Health and Human Development.

Long-term commitment of people

The research and development process requires scientists who are both willing and able to devote years to the pursuit of leads, many of which may fail before one is found that succeeds. When the pharmaceutical industries in the USA and in Europe reduced their investment into new contraceptive research in the 1970s, the role of public-sector and nonprofit organizations in this type of activity had to be expanded.

The Council's biomedical research facilities, small and low key at the beginning, have undergone great changes over the years in response to the need for more direct involvement in contraceptive development. Its scientific capacity expanded in two ways. In 1970, the Biomedical Division was enlarged to include administrative and regulatory experts as well as research scientists. A year later, the ICCR was created as a centrally managed, international team of independent clinical investigators who help to shape and accelerate research projects.

Working closely with Council scientists to pursue and review the progress of potential new leads, ICCR members present their research results several times each year. Frequently, participants at such meetings also include scientists from such bodies as WHO, USAID, and other public-sector groups involved in conducting or contributing to contraceptive research, and representatives of private pharmaceutical companies.

Harold Nash, senior scientist at the Center for Biomedical Research and coordinator of the NORPLANT project, considers this approach valuable. "Having a multifaceted team to handle all parts of the development process is a tremendous advantage over an operation that contracts out different units of work." He goes on to says that "having our own laboratory resources, for example, allows a flexibility of response to new findings that simply can't be achieved when new contracts must be negotiated every time new directions are called for."

> "The ICCR provided an international core of investigators to conduct and coordinate the development process. These scientists combined a broadly based dedication to the success of the program with critical but knowledgeable guidance."
> *Harold Nash*

To introduce NORPLANT, the Council had to expand its social and health science capability by adding staff as well as by establishing a worldwide network of consultants. Through collaborative ties with individuals and other nonprofit institutions, the Council could call on the experience of people from both developed and developing countries trained in social science and clinical research, the development of information materials, and women's health issues.

Coordinating regulatory filing with introduction

The regulatory requirements of many countries have become more demanding in recent years. In the USA, preparation of the New Drug Application for the FDA required the collection of huge amounts of clinical data from around the world. In addition, the Council underestimated the number of staff and the amount of time needed to organize the field-trial results and fulfill the requirements of the regulatory agencies. The late filing and the resultant late approval for marketing delayed the implant introduction and distribution process for more than 1 year.

Because regulatory approvals are critical to all subsequent introduction and incorporation steps, it is important to establish a timetable to permit a smooth transition from research and development to introduction and marketing. The timing for the introduction of a product

depends to a certain extent on when the application for registration is filed. Sufficient staff and time must be allocated to the application process, with attention given to standardizing record forms for all the clinical data. In addition, final descriptions of the characteristics and performance of a product in all training and information materials must be consistent with the final labeling language approved by the regulatory authorities.

Long-term commitment of funds

The development, introduction, and incorporation of a new contraceptive method requires an enormous amount of money over a long period. This kind of funding needs donor support for general research and program efforts, as well as for specific country programs.

The international clinical studies needed to assess the 5-year performance of NORPLANT took many years to design, conduct, monitor, and evaluate, a task that depended on a continuously funded and organized Council/ICCR team. Similarly, introduction and incorporation require sustained funding for staff to manage and coordinate programs, participate in training and orientation meetings, and collaborate in producing information materials.

It is impossible to assess the costs and benefits of the NORPLANT program accurately. In scientific investigation, where some contraceptive leads come to fruition and some do not, it is difficult to distribute the costs among projects. The method used to safety test levonorgestrel for NORPLANT might be useful for future contraceptive methods that contain the same hormone and are developed by other organizations. In addition, there are costs that do not show up in the Council's balance sheets, such as those incurred by private-sector partners or collaborating public-sector organizations.

The Council estimates that it had invested 18.5 million USD in NORPLANT by the end of 1988: 2.6 million in research, 7.7 million in development, and 8.2 million in introduction and incorporation into family-planning programs. Other public-sector investments in the NORPLANT method, especially during the introduction stage, were made by collaborating agencies and by local institutions in developing countries. All this is relatively cost effective when compared with estimates from the pharmaceutical industry of 40–70 million USD over a

20-year period for developing a new contraceptive from the idea to the final approved product.

Ultimately, the return on this investment must be judged in terms of the contribution the method makes to meeting the contraceptive goals of couples around the world. The ready acceptance of NORPLANT in introduction programs — with continuation rates as high as 90% in the 1st year and about 40% after 5 years — indicates that the return in these terms will be impressive.

The Council believes that its activities in developing contraceptives will contribute to a reduction of unwanted pregnancies and an improvement in maternal and child health, benefits that are very difficult to quantify globally.

Designing a plan for a smooth transition

Although it is impossible to plan for all contingencies, the NORPLANT experience has shown that it is important for an organization to devote time and effort at an early stage to formulating a statement of purpose and goals, a detailed outline of projected activities, and a strategy to accomplish them. It is equally important that the plan be flexible and the planners responsive to changing conditions.

The strategy for introducing NORPLANT underwent substantial review at the Council, accounting for the method's characteristics, its service-delivery requirements, and the users' needs. Rather than promoting any specific contraceptive method, the Council stresses the broader objective of ensuring better use of family-planning services. As a result, the Council embraced a user-oriented rather than a method-specific approach to family planning. In addition, a focus on the total contraceptive behaviour of couples indicates a need for, and accounts for the practice of, switching between methods. This perspective required a nonpromotional approach to NORPLANT introduction.

From the outset of the introduction program, it was clear that NORPLANT would be both a training-intensive and service-intensive method. The niche that NORPLANT fills in the family-planning "cafeteria" of methods depends heavily on the ability of service-delivery systems to adapt to specific requirements. Mechanisms must be put into place to provide trained staff, facilities, supplies, information for counseling, record keeping, and clinic practices to make this new contraceptive easily available and to manage any problems that users might experience.

"Being parent to the method means being parent to the introduction process as well."
Forrest Greenslade

Above all, the NORPLANT project has made people aware of the relationship between scientific inquiry in a laboratory to develop a method and that method's eventual use and acceptance in the world. The success of the project has underscored the link between the biomedical, social, and health sciences in making available to women an innovative, effective, acceptable family-planning method that meets a real need.

It is likely that some aspects of the NORPLANT program will become the standard for developing and introducing contraceptives. Certainly the Council has demonstrated that collaboration among nonprofit- and private-sector scientists, organizations, and companies can result in new-product development — provided that ample and continuous funding is available, for both basic research and clinical trials. The NORPLANT program also demonstrates the importance of preintroduction trials for training and data collection, and emphasizes the need for counseling, research on both the users and the program, and providing balanced information.

Looking to the future

More than 20 years have passed since Sheldon Segal and Horacio Croxatto began investigating the properties of silicone rubber. By 1989, 6 years after the introduction program formally got under way, NORPLANT had been accepted as an important new contraceptive. However, the method is not likely to revolutionize the contraceptive field the way the birth-control pill did.

"NORPLANT very definitely fills a need for a long-term method that doesn't require constant attention," says Beverly Winikoff, a Council physician and public-health specialist who has played an important role in the introduction program. "But women will still want more contraceptive choices to meet their changing requirements. NORPLANT is a good alternative to sterilization. It is an excellent way to space children. It works well for women who want no more children, yet have a decade or two of reproductive potential ahead of them. But it is not the solution for short-term spacing or for women who do not want a hormonal method or who cannot tolerate the bleeding irregularities."

That means continuing the search for new methods. The developers of NORPLANT recognize that the subdermal

Counseling potential users about available methods of family planning in Nigeria.

"The most important component of the NORPLANT program is counseling.... Women deserve a good explanation of all NORPLANT's effects .... This is important because, if she comes down with a virus or a sore toe, she knows her symptoms have nothing to do with the method. Nor, on the other hand, can she attribute her good luck to NORPLANT if she wins in the lottery."
Francisco Alvarez-Sanchez

implant is no panacea, and that acceptance of any method implies certain tradeoffs. A woman must choose between a higher level of protection against pregnancy and potentially more uncomfortable side effects, or a less effective method with perhaps fewer side effects. If resupply is a problem, a one-time, long-acting method may be preferable to the use of pills or injections.

These decisions are not easy ones; frequently the user opts for one solution only to learn after an initial period of use that she is not comfortable with her choice or that her circumstances have changed and that she may desire another pregnancy. Family-planning programs must be responsive to such possibilities with the various methods they provide. Women change birth-control methods more than once in their reproductive lifetimes and this should be anticipated in the clinic.

Still, women's reactions to NORPLANT have been better than some expected. Wayne Bardin, director of the Council's Center for Biomedical Research and a Vice-President of the Council, recalls that many initially doubted the method's future. "In retrospect, some remember the NORPLANT development as one smooth continuum, but it was never that sharp and clear."

In 1979, when Bardin succeeded Sheldon Segal at the Center, he says, "There was a great deal of opposition to implants from population experts who were convinced women would never accept the method. Even I had doubts. But, as the results of the multinational trials came in, we saw how incredibly effective the method was, more effective than doctors had imagined, and at the same time how convenient it was. Women who had the implants removed wanted new ones inserted."

Other potential methods

Several new contraceptives are in the research and development pipeline or in early stages of introduction. Most of them are being pursued either by the Council or one of the other nonprofit research organizations that are developing new methods. The future may see variations on the implant concept — the two-rod NORPLANT-2, a one-capsule system, or biodegradable pellets, for example. Other possible future methods include contraceptive rings, progestin-releasing intrauterine devices, hormone-releasing skin patches, improved injectables and barrier methods,

antifertility vaccines, nonsurgical methods to terminate early pregnancy, and male contraceptives, including vaccines and vasectomy performed without a scalpel.

It is unlikely that any of these methods will dominate family planning as The Pill once did. Each new method, however, will fit a niche in the array of family-planning methods that is available, offering more couples greater choice.

Including the Council, only a handful of organizations is responsible for most of the nonprofit sector's contraceptive development at present. Because no one organization is capable of doing all the contraceptive development and introduction activities alone, these agencies frequently collaborate. Several are part of the NORPLANT effort, as described in the chapter "Plans, priorities, and partners." Others not mentioned earlier include:

- The Contraceptive Development Branch of the Center for Population Research, National Institutes of Health and Human Development, a US funding agency for contraceptive development, has worked on complete contraceptive development since 1969.
- WHO's Special Programme of Research, Development and Training in Human Reproduction (HRP) was established in 1972. In addition to conducting clinical research, HRP/WHO plans to introduce its own new methods. In its 1986/87 annual report, HRP/WHO notes this change in strategy came about because, in recent years, "the pharmaceutical industry has begun — for various reasons — to move away from the field of fertility regulation and to reduce or cease involvement. This imposes on the Programme the burden of introducing the new methods and of seeking the necessary funding."
- The Contraceptive Research and Development Program of the Eastern Virginia Medical School was established in 1986 to identify and develop new leads in contraceptive technology through applied fundamental research, clinical studies, and product design and development.
- The Developing Country Population Initiative, formed in 1987, conducts clinical trials.

In addition, some governments have their own medical research councils that conduct contraceptive development focusing on national needs.

Appendices

Characteristics of NORPLANT implants

General description

NORPLANT is an effective, long-lasting, reversible contraceptive that provides protection for 5 years. Six thin, flexible capsules made of a soft rubber-like material and filled with a synthetic hormone are inserted just under the skin of a woman's upper arm in a minor surgical procedure. Protection is provided within hours of insertion and the woman rapidly returns to her normal fertility when the implants are removed. The most common side effect is change in the pattern of menstrual bleeding.

Components

NORPLANT is not made of new ingredients. What is new about NORPLANT is the way it delivers the contraceptive drug into the body. Each of the six flexible NORPLANT capsules is 34 mm long and 2.4 mm wide and contains 36 mg of levonorgestrel, a synthetic progestin widely used in combined oral contraceptives and in The Mini-Pill. The progestin diffuses through the walls of the capsules in continuous low doses. The silicone rubber tubing has been used in surgical applications since the 1950s. The NORPLANT system is made possible by the ability of the Silastic tube to release levonorgestrel for at least 5 years.

Research and testing

NORPLANT has undergone more than 20 years of extensive research and testing both in developing and developed countries. To date, more than 55 000 women in more than 44 countries have used NORPLANT in clinical trials and preintroduction evaluations. An additional 400 000 sets of capsules have been distributed in the 13 countries where NORPLANT has been approved for general use.

Effectiveness

NORPLANT is one of the most effective reversible contraceptives. No contraceptive is totally effective but fewer than 1 in every 100 women who use NORPLANT for a year will become pregnant. That is a lower failure rate than for The Pill or most IUDs, and can be compared to surgical sterilization during the first 3 years of use. It should be noted, however, that there is a correlation between effectiveness and a woman's weight. After the 2nd year, heavier women, particularly those who weigh more than 70 kg (or 154 lb), have a higher probability of becoming pregnant than lighter women.

Duration of effectiveness

NORPLANT becomes effective within a few hours of insertion and will provide contraceptive protection for 5 years. All six capsules must be inserted at the same time, even if the method is to be used for fewer than 5 years. At the end of the 5th year, the implants become less effective and should be removed; a new set may be inserted for continued protection.

Mechanism of action

Pregnancy is prevented through a combination of mechanisms. The most important ways are by inhibiting ovulation, so that eggs will not be produced regularly, and by thickening the cervical mucus, making it more difficult for the sperm to reach the egg. Other mechanisms may add to these contraceptive effects.

Appropriate candidates for NORPLANT

NORPLANT may be used by almost any woman in her fertile years who wants to avoid becoming pregnant. It is particularly suited for women who are seeking continuous contraception, women who want to space their children, women who cannot use methods that contain estrogen or who do not want to be sterilized, and women who desire a method that is convenient and not related to sexual intercourse.

Women who should not use NORPLANT

Some women should not use NORPLANT. For example, NORPLANT should not be used by women who have active thromboembolic disorders, undiagnosed abnormal genital bleeding, acute liver disease, benign or malignant liver tumours, or known or suspected carcinoma of the breast.

Women who are pregnant should not use NORPLANT. If a woman becomes pregnant, the implants must be removed immediately.

Cigarette smoking increases the risk of serious cardiovascular side effects from combined oral hormonal contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes/day), and is quite marked in women over 35 years of age. Although this is believed to be an estrogen-related effect, it is not known whether a similar risk exists with progestin-only methods such as NORPLANT.

Warnings based on experience with NORPLANT

Functional ovarian cysts (generally asymptomatic, but palpable by clinicians) sometimes occur in NORPLANT users. They usually disappear spontaneously and should not require surgery. Rarely, they may twist or rupture so that surgical intervention is required.

Although pregnancy is rare, there is a chance that it could be ectopic. Clinical studies have shown no increase in the rate of ectopic pregnancies per year among NORPLANT users as compared with users of IUDs or those who use no contraceptive method. The incidence among NORPLANT users was 1.3/1 000 women per year.

The risk of ectopic pregnancy may increase with the duration of NORPLANT use and possibly with increased weight of the user.

Other considerations

Women with any of the following conditions should be checked regularly by their health-care provider if they choose NORPLANT: breast nodules, fibrocystic disease of the breast, and abnormal breast X-ray or mammogram; diabetes; elevated cholesterol or triglycerides; high blood pressure; migraine or other headaches; epilepsy; mental depression; gallbladder, heart, or kidney disease.

The health-care provider should also determine if the woman smokes or is taking any medications.

Use by lactating women

Studies have shown no significant effects on the growth or health of infants whose mothers use levonorgestrel implants beginning 6 weeks after childbirth. However, steroids are not considered the contraceptives of first choice for breastfeeding women.

Interaction with other drugs

Certain drugs may affect the metabolism of the hormone delivered by NORPLANT making the implants less effective in preventing pregnancy. These include rifampin, phenylbutazone (Butazolidin is one brand), and drugs used for epilepsy such as barbiturates (for example, phenobarbital) and phenytoin (Dilantin is one brand). The health-care provider should be aware if the woman is taking any of these medications.

Timing of insertion

To make sure the woman is not pregnant, NORPLANT should be inserted within 7 days after the onset of menstrual bleeding, or immediately post abortion.

Visibility of the capsules

Because the incision is tiny and there are no sutures, NORPLANT does not leave a noticeable scar in most women. The implants usually are not visible. When they are, they can be seen underneath the skin and resemble veins. The implants will not move around and will remain under the skin where they are placed. They are flexible and cannot break inside the woman's arm. The user does not have to be concerned if the implants are bumped or if pressure is put on the area when, for example, a child is carried. After the incision has healed, the skin over the implants can be touched at any time.

Common side effects

Most side effects of NORPLANT are not serious. The most frequently reported side effect is a change in the pattern of menstrual bleeding. Irregularities vary from woman to woman and may include: prolonged menstrual bleeding during the 1st month of use, longer bleeding than a woman would normally experience;

untimely bleeding or spotting between periods; no bleeding at all for several months or, for a few women, for 1 year or longer; or a combination of these patterns.

The kind of a bleeding pattern a woman will have cannot be predicted. Many women can expect an altered bleeding pattern to become more regular after 9–12 months. Despite the increased frequency of bleeding in some women, the monthly blood loss is usually less than during normal menses. In most studies, in fact, hemoglobin levels of NORPLANT users have been shown to rise.

In addition, women using NORPLANT have complained about the following conditions, which may be related to the method: headache (the most frequent complaint after menstrual irregularities), nervousness, nausea, dizziness, adnexal enlargement, dermatitis (inflammation of the skin), acne, change of appetite, mastalgia (breast tenderness), weight gain, hirsutism (excessive facial hair growth), and hair loss.

Existing conditions of acne, or excessive growth of facial or body hair, may be worsened. Occasionally, an infection may occur at the implant site, or there may be a brief incidence of pain or itching.

A number of other complaints reported by NORPLANT users or discovered by physicians may or may not be associated with the method. These include breast discharge, cervicitis (inflammation of the cervix, detected by physician), mood change, depression, general malaise, weight loss, pruritis (itching), and hypertension.

Although the clinical experience is still insufficient to detect rare adverse events, there is no evidence of cardiovascular, respiratory, central nervous system, or other serious problems, nor is there any evidence of carcinogenicity associated with NORPLANT use. There is no evidence of teratogenicity in the NORPLANT clinical experience.

Insertions and removals

Any specially trained physician, nurse, nurse-midwife, or other trained health worker can do the insertion and the removal. NORPLANT implants are inserted under the skin of a woman's arm in a minor surgical procedure performed under aseptic conditions. A local anesthetic is injected into the upper arm. A small incision is made — only 2 mm long — and the capsules are placed one at a time with a special needle just under the skin in a fan shape. The procedure should take no longer than 10–15 minutes. Because local anesthetic is used, there should be little or no pain. Usually, the incision is covered with a small adhesive bandage and protective gauze.

Just as for the insertion, the capsules are removed in a minor surgical procedure under aseptic conditions. The health-care provider applies a local anesthetic. A small (4-mm) incision is made through which all the capsules are removed. Removals may be more difficult than insertions. The removal process usually takes 15–20 minutes, but may take longer if some of the capsules are difficult to locate. If the health-care provider is not able to remove

all the capsules at one time, the woman may be asked to return to the clinic.

If the woman wants to continue using NORPLANT, a new set of implants can be inserted at the same time the old set is removed. If the woman does not want to continue with NORPLANT and does not want to become pregnant, she should be offered another contraceptive method before she leaves the clinic.

Return to the clinic

The woman should be encouraged to return to the clinic if she has any problems with the method that worry her, if she wants to have a child, or if she is moving away from the area and needs the address of a clinic in her new area that provides NORPLANT services.

Warning signs of possible problems

The NORPLANT user should go to her health-care provider or clinic right away if she has severe lower abdominal pain; heavy vaginal bleeding; arm pain; pus or bleeding at the implant site; expulsion of an implant; episodes of migraine, repeated severe headaches, or blurred vision; or delayed menstrual cycles after a long interval of regular cycles.

Reversibility

One of the most important characteristics of NORPLANT is that it is reversible. The contraceptive action ceases quickly when the implants are removed. Access to prompt removal is important and this is emphasized as part of the training of NORPLANT providers.

Pregnancy rates after removal

Once the implants are removed, the contraceptive effect ceases within 24 hours and the woman can become pregnant as rapidly as women who have not used the method. Rates of pregnancy for women who had NORPLANT removed for planned pregnancy are similar to those for women using no contraception.

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Head Office
IDRC, PO Box 8500, Ottawa, Ontario, Canada K1G 3H9

Regional Office for Southeast and East Asia
IDRC, Tanglin PO Box 101, Singapore 9124, Republic of Singapore

Regional Office for South Asia
IDRC, 11 Jor Bagh, New Delhi 110003, India

Regional Office for Eastern and Southern Africa
IDRC, PO Box 62084, Nairobi, Kenya

Regional Office for the Middle East and North Africa
IDRC/CRDI, PO Box 14 Orman, Giza, Cairo, Egypt

Regional Office for West and Central Africa
CRDI, BP 11007, CD Annexe, Dakar, Senegal

Regional Office for Latin America and the Caribbean
CIID, Casilla de Correos 6379, Montevideo, Uruguay

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